Science Council of Canada
Conseil des sciences du Canada

REPORT 42

GENETICS IN CANADIAN HEALTH CARE

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The photographs on the front cover show two sisters from Quebec. Both were born with phenylketonuria (PKU). The sister on the left was born in 1962. Her condition was not discovered early enough to prevent severe mental retardation. Her younger sister, shown on the right, was tested for PKU and diagnosed when three days old. She was placed on a diet low in phenylalanine, and her development was unimpaired. Today she is able to lead a normal life. Screening programs that enable diagnosis and treatment of all newborns with PKU are now in place throughout Canada.

REPORT 42

GENETICS IN CANADIAN HEALTH CARE

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The Publications Office
Science Council of Canada
100 Metcalfe Street
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The Honourable William C. Winegard
Minister for Science
House of Commons
Ottawa, Ontario

Dear Dr Winegard:

In accordance with Section 13 of the Science Council of Canada Act, I take pleasure in forwarding to you the Council's Report No. 42, *Genetics in Canadian Health Care*.

This report explores the implications of applying genetic knowledge to improve the health of Canadians. It has been carried out in the framework of the Science Council's mandate:

> To assess the scientific and technological resources, requirements, and potentialities of Canada;
>
> To increase public awareness of
> - scientific and technological problems and opportunities;
> - the interdependence of the public, governments, industries, and universities in the development and use of science and technology.

Many of the issues dealt with in this report go well beyond the technological, as a matter of necessity. The complex ethical and legal issues associated with development and use of genetic technologies raise fundamental questions about our values and attitudes regarding human health.

This report raises profound public policy questions, but it does not pretend to have all the answers. There must be further public debate on the controversial questions surrounding the integration of genetics into the health care system. This report aims to catalyse that debate.

Yours sincerely,

Janet E. Halliwell
Chairman
Science Council of Canada

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PREFACE

Advances in science and technology are improving our understanding of the many factors affecting health and constantly generating new ways to prevent and treat disease. A major challenge is to ensure these advances are used in a way that maximizes their benefits and minimizes any potential harm.

In 1986 the Science Council of Canada launched a project to review the current and potential role of genetic knowledge and technologies in Canadian health care. The goal was to examine the related policy issues and to stimulate progress in addressing them.

The project's findings, presented in this report, are based on a comprehensive program of policy research and consultation. More than 200 people participated in the project: experts in law, education, medical ethics, health care economics, and science policy, as well as in medicine and medical research. Also consulted were 47 associations representing Canadians with diseases with possible genetic causes.

Genetics in Canadian Health Care focuses on the issues surrounding the development and application of genetic health services. However, the Science Council recognizes that genetic make-up is only one of many factors — biological, environmental, and social — that contribute to disease. Moreover, there are a number of approaches to preventing and treating disease. They include, for example, reducing poverty and improving the work environment as well as new surgical techniques and medications.

The Science Council acknowledges, too, that there is enormous competition for resources in the health care field. Genetics issues merit attention on several counts:

- the importance of genes as a causal factor in disease is increasing as other factors are better controlled;
- genes are being implicated in an increasingly wide range of disorders;
- genetic knowledge and technologies have the potential to profoundly affect the health of Canadians;
- genetic knowledge and technologies also raise complex ethical and technical questions that need to be addressed.

The goals and initiatives presented here provide a framework upon which effective and ethical development of genetic services can proceed. It is up to each reader — policy maker, planner, educator, health provider, or patient — to take the next steps to ensure that health care in Canada continues to evolve as a reflection of a caring society.

1. OVERVIEW

Good health is the bedrock on which social progress is built.
A nation of healthy people can do those things that make life worthwhile,
and as the level of health increases so does the potential for happiness.
Marc Lalonde
A New Perspective on the Health of Canadians

Maintaining good health goes far beyond reasonable access to competent medical care. And it goes beyond adequate nutrition and what is considered a "healthy" lifestyle. Many factors have an impact on how we feel and how we resist illness. In a significant way, our environment, family relationships, social, cultural, economic, and work conditions — even our self-esteem — determine who gets sick and who stays healthy.[1] The way all these factors interact is subtle, complex, and not fully understood, although scientific advances are constantly leading to better understanding of the nature and causes of specific diseases. Similarly, technological advances are leading to better methods of preventing, diagnosing, and treating particular diseases.

Numerous factors affect maintenance of good health.

This report is about the role of one factor — our genes — in health and disease, and the implications of genetic knowledge and technologies for personal and collective health and for delivery of health care in Canada.

Genes are one factor that affect health and cause some of our diseases.

We are in the early stages of a revolution in medical science. The application of new biotechnologies to human genetics is resulting in a quantum leap in our understanding of the nature and function of the human organism, and of the mechanisms of disease. The new genetic technologies are making it possible to recognize individuals with genetic diseases or at risk of developing them, and provide the basis for the development of effective prevention and treatment measures. Health services based on these technologies, when available for voluntary use by individuals and families, offer potential health benefits to Canadians.

New genetic technologies are providing the basis for development of effective prevention and treatment measures...

But along with the benefits, genetic technologies, and the information they produce, have the potential to be misused.[2] Inappropriate applications can result in harm to individuals and could adversely affect future generations.

...but also have the potential to be misused.

We are only beginning to develop genetic health care services based on the new technologies. But it is already evident that there is a need for changes in Canada's health care and education systems and for more research if we are to maximize the health benefits of genetic knowledge and technologies. There is an equally strong need to ensure that the development and application of genetic technologies proceed carefully. Clear objectives for the use of the technologies are required, along with guidelines and, where appropriate, controls. Potential technical and ethical problems must be identified and dealt with as research and development proceed.

To maximize the benefits and avoid misuse of genetic technologies, wise planning and changes in our health care and education systems are needed.

Role of Genes in Health and Disease

Genetic technologies are providing the opportunity to address the biological elements of health and disease.

It is generally accepted that maintenance of good health involves four interrelated factors: human biology, environment, lifestyle, and the health care system, all of which must be continually addressed in an integrated and balanced manner.[3] However, there are times when one or another of these factors offers a particular opportunity to understand and deal with specific health problems or improve general health status. Today, genetic technologies are providing the opportunity to address more fully the biological elements of human health and disease.

Information is accumulating on genes, the biological processes they encode, and the diseases they can cause.

The new recombinant DNA technologies provide the technical breakthrough that allows the isolation and analysis of genes, and thus enables the search for the genetic basis of disease to occur directly at the DNA level. These technologies are leading to a growing understanding of how genes contribute to our state of health and cause or make us susceptible to some diseases[4] (see Box 1). Because of these new technologies, information is accumulating on the specific DNA sequences of genes, the biological processes they encode, and the diseases and disease processes they can cause.

Individuals have a unique genetic make-up that influences their susceptibility to diseases.

Some genetic disorders are inherited, resulting from mutations in the DNA of previous generations. In other cases genetic disease is not inherited but results from mutations in the body cells of an individual; the subsequent disorder may or may not be transmitted to offspring. The combined processes of inheritance and mutation lead to genetic variation between individuals. One consequence of this variation is that individuals each have a unique genetic make-up that influences their diseases and disease susceptibilities.

Genes are implicated in many common diseases not usually thought of as genetic.

The ways in which genes contribute to disease vary. The general public, most patients, and many health care providers tend to think of genetic disease largely in terms of classic, often rare, single-gene disorders such as haemophilia, Huntington disease, or cystic fibrosis. In these single-gene disorders the presence of a specific gene will invariably lead to onset of the disease. However, genes are also implicated in many common diseases not usually thought of as genetic. These diseases are multifactorial; that is, genes make the individual susceptible to disease, but disease onset is triggered by some external environmental factor. Examples include some forms of arthritis, diabetes, Alzheimer disease, cancer, manic depressive illness, alcoholism, and heart disease. These diseases are more difficult to understand than the single-gene disorders.

Genetic Disease and Its Implications in Canada

The relative significance of "genetic" disease has increased.

Genetic disease contributes in a substantial way to the burden of ill health in Canada. With improvements in social conditions and public health and medical practices we have experienced a relative decline in the incidence of diseases caused by infection and nutritional deficiencies. As a result, the relative importance of "genetic" disease has increased.[5] Today, even based on our current limited knowledge of gene-disease links, it is estimated that at least one in 20 Canadians will experience a gene-related impairment, disability, or handicap by age 25[6] and that during their lifetime more than half the population will have a disease that in some cases has a genetic component to its cause.[7] For example, many of the chronic diseases of middle and old age appear to be multifactorial and have a genetic component.[8] Up to half the admissions to

paediatric hospitals[9] and 12 per cent of adult admissions to general hospitals[10] are for "genetic" diseases. And an important but undetermined share of psychiatric admissions have some genetic link.[11]

In recent years, the number of diseases for which genetic causes have been identified has increased exponentially. Genes are now known to contribute to several thousand diseases. In addition, some diseases and mutations occur at higher incidence in specific regions of Canada or subgroups of the population. This clustering of disease reflects biological, cultural, and environmental factors. As we learn more and more about the causes and clustering of diseases, we can increasingly use the knowledge to develop prevention and treatment measures.[12]

Genes are now known to contribute to several thousand diseases.

Strategies for Dealing with Genetic Disease

The growing understanding of the role of genes in all aspects of health and disease has broad implications for health care delivery. Genetic knowledge and technologies have applications in diagnosis of disease and in strategies for fighting disease through prevention, treatment, avoidance, and gene therapy.

Genetic technologies offer potential strategies to fight disease.

Diagnosis of individuals with or at risk for genetic disease is a critical first step in providing prevention or treatment options. Now, in addition to diagnostic technologies based on clinical signs and indirect methods of detecting genetic disease, recombinant DNA technologies can be used to analyse DNA and detect genes that cause or are associated with disease.

Prevention of disease is the ideal strategy. Genetic technologies are contributing to prevention of disease through identification of environmental risk factors and healthier lifestyle options for individuals at risk. Measures that reduce the mutation rate constitute primary prevention, and include control of exposure to ionizing radiation and chemical mutagens. Where a mutation has already occurred or been inherited, secondary prevention addresses the interacting risk factors for genetically susceptible individuals — for example, controlling diet for those at risk for heart disease.

Genetic technologies are helping to prevent disease.

Where prevention is not possible, the strategies include treatment to address the consequences of the mutation, avoidance of the birth of children with serious genetic diseases, and gene therapy to offset or correct the mutation.

Where prevention is not possible, strategies include treatment, avoidance, and gene therapy.

An improved ability to identify individuals at genetic risk can lead to earlier diagnosis and treatment, and thus a better prognosis (as in the case of some familial cancers). In addition, understanding the underlying genetic causes of a disease and the metabolic processes under way in the course of the disease can help in the development of effective treatments, including medications.

A number of avoidance strategies are available for families that are at risk of having children with serious genetic disorders. Avoidance-based strategies include deciding not to have a family, prenatal diagnosis (with the option of pregnancy termination if the fetus is affected), and alternative avenues to parenthood. Alternatives include adoption, artificial insemination, and other reproductive technologies.

Gene therapy involves correcting the intrinsic defect in the genetic material. No proven gene therapies are available to cure genetic disease at this time, but

Box 1:
Genes, Mutation, and Disease

Modern human genetics evolved from centuries of scientific exploration into the causes and treatment of inherited diseases. In 1953, James Watson and Francis Crick's landmark work[1] on the nature of deoxyribonucleic acid (DNA) provided the key to understanding the complex links between genes and disease. It is now understood that:

- DNA molecules are made up of chains of nucleotides bound together in a double helix. DNA molecules and the information they carry on some 50 000 to 100 000 genes control the structure, organization, and function of cells.
- A gene is a specific stretch of the DNA molecule and codes information for production of a specific protein. It is the specific nucleotide sequence of the gene that provides the code.
- Genes are transmitted from parent to offspring and are the mechanism for inheritance. An important feature of genes is their ability to be replicated identically and transmitted from generation to generation. But genes can also be altered: the nucleotide sequences along a DNA molecule are susceptible to change through a process known as mutation.
- Mutations may occur during the process of cell division to produce eggs and sperm, through exposure to specific environmental factors that cause mutation, or as a consequence of spontaneous change.
- In many cases a change in the DNA sequence of a gene will result in malfunction of the gene and disease in the organism.
- An individual's full complement of DNA is referred to as his or her genome and is normally identical in the nucleus of every cell in the body.

research will undoubtedly yield gene therapy for some disorders. There are two forms of gene therapy, one involving germ line cells, which can be inherited, the other somatic (i.e., body) cells, which affect the health of the individual but are not transmitted to the next generation. In September 1990 a four-year-old American girl became the first person to undergo somatic cell gene therapy in an attempt to treat a genetic disorder (severe combined immune deficiency disease), and research involving such treatment is under consideration for a number of other disorders. But gene therapy is complex and bears risks as well as potential benefits, both to the individual being treated and, in the case of germ line therapy, to future generations. It is therefore imperative to proceed very carefully.

Although genetic technologies are already being used to prevent, treat, and avoid diseases, we are still in the early stages of acquiring genetic knowledge and developing related health care applications. In most cases we do not yet fully understand the role our genes play in either single-gene or multifactorial disorders and have not yet identified specific mutations that allow accurate identification of individuals with or at risk for specific disorders. Moreover, at present our ability to identify an individual at risk for genetic diseases exceeds our ability to prevent or treat the disease.

We are still in the early stages of acquiring genetic knowledge and applying it to health care.

If we knew the specific mutations resulting in single-gene disorders we would be closer to developing effective treatments and even gene therapy solutions. Similarly, if we knew which genes make us susceptible to particular multifactorial disorders, we could determine what external factors are required to trigger onset of disease. We could then use the information to prevent or delay onset and to develop more effective treatments.

Despite their potential benefits, genetic technologies must be developed and used cautiously. Research related to human genetics should be subject to guidelines and review procedures that incorporate ethical and safety considerations to protect the human participants and the environment. Similarly, the introduction of any new genetic tests or treatments for clinical purposes should conform to appropriate guidelines, and should proceed only after a comprehensive technology assessment that incorporates technical, safety, ethical, societal, legal, and economic considerations.

Despite their potential benefits, the technologies must be developed and used with caution.

Delivery of Genetic Health Care Services

For over half a century genetic services, including screening and testing, counselling, and follow-up treatment programs, have had a place in Canadian health care systems. In fact, Canada has been a pioneer in the development and delivery of genetic health services. Thanks to genetic technologies and services, some single-gene diseases have become virtual "non-diseases" for the affected patients. For example, individuals with phenylketonuria can now grow up and lead normal lives, whereas only 30 years ago they would probably have been confined for life to institutions for the mentally retarded. Yet, despite such successes, genetic technologies and services are not well integrated into Canadian health care.

Canada has been a pioneer in developing genetic health services but overall, genetic technologies and services are not well integrated into Canadian health care.

There are two important, interrelated approaches to delivering genetic services. One approach involves the delivery of specialized services (usually targeted to single-gene disorders) through genetic centres. The second approach involves the integration of genetic knowledge and technologies into the routine

There are two approaches to delivering genetic services.

practice of all aspects of medicine. For example, many of the common multifactorial diseases require solutions that involve prevention as well as treatment; genetics has a role to play in understanding these disorders and in contributing to solutions.[13]

Genetic centres cannot meet even the current demand for services.

In Canada, there are eight major centres accredited by the Canadian College of Medical Geneticists for genetics training and comprehensive service delivery. In addition, there are twice as many centres offering some specific genetic health services. A survey of 10 Canadian genetic centres in 1986-87 indicated that eight of the centres could not meet the current demand for services, let alone the increased demand anticipated as a result of new DNA-based technologies and growing public awareness of the benefits of genetic services.

Funding is the principal limitation. The centres experience particular difficulty in obtaining funds to deliver new technologies, even those that can be demonstrated to be beneficial and cost effective.

Moreover, health care practitioners are not incorporating genetic knowledge and tools into their practices.

Not only are the genetic centres constrained in their ability to deliver services, but physicians and other health care practitioners are not effectively incorporating available genetic knowledge and tools into their practices. The integration of genetic technologies into routine health care practice is limited partly by the scarcity of knowledge and technologies and partly by a general lack of awareness regarding available technologies and their applications and benefits.[14] Genetics has implications for all aspects of health care, beginning with an understanding of why a patient has a particular disease. If the Canadian public is to reap the benefits of genetic knowledge and technologies, all health care practitioners must become, to some degree, "geneticists."

Some progress toward integration is being made...

Some progress toward better integration of genetics into health care delivery is being made. Several provinces have established provincial advisory committees on genetic services. The committees raise awareness and assist in the efficient allocation of services. In addition, non-governmental organizations — such as the Canadian Cystic Fibrosis Foundation and the Huntington Society of Canada — provide research funding, maintain a strong advocacy role in their dealings with health ministries and professional organizations, and offer services relevant to specific disorders.

...but improvements are needed.

Despite these efforts, improvements are needed in how genetic health services are integrated into health care. These improvements will require diverse changes in public policy, in medical practice, and in education of the public as well as health care planners and providers; and thorough evaluation of the effectiveness, reliability, costs, and benefits of specific genetic services. All these improvements and indeed all planning for both current and future genetic health services must include ethical considerations.

An Ethical Context

Ethical issues associated with genetics are of particular concern.

If not used properly, genetic technologies and the information they provide could result in harm. The ethical issues associated with genetics are of particular concern because in the past, serious abuses of human rights occurred in the name of eugenics; for example, genetics has been used to justify claims of racial superiority or inferiority and to discriminate against individuals.[15] Care and planning are required to prevent any recurrence of such abuses and to

ensure that the full range of ethical issues associated with genetic research, technologies, service delivery, and information are satisfactorily addressed.

Diagnostic testing (which identifies individuals with or at risk of disease), population screening (to identify carriers of harmful genes), prenatal diagnosis, gene therapy, DNA banks, and disease registries raise a variety of concerns. Among them are the possibility that individual choice in health care decisions will be lost, or that the confidentiality of health records and information will not be maintained. In addition, there are ethical concerns associated with the general issue of tampering with our essential "humanness."

There is a concern that individual choice will be lost or that the confidentiality of health records will not be maintained.

Non-medical applications of genetic technologies also raise concerns Potential non-medical uses include fetal sex selection, exclusion of individuals from employment or insurance coverage, proof of kinship or paternity for legal or immigration purposes, and development of agents for biological warfare.

All of these concerns point to a need for open, ongoing discussion of the ethical issues surrounding genetic technologies and applications. Many of these issues are complex and evoke a wide range of opinions among Canadians. Different perceptions of what is good for the individual and what is good for a society that has universal health insurance are likely to drive vigorous debate. Such debate is necessary to set suitable goals, to identify and deal with conflicts, and to generate appropriate objectives, standards, guidelines, and controls.

Open, ongoing discussion of the ethical issues is necessary to set goals and establish appropriate guidelines, standards, and controls.

A major component of a compassionate health care system is its understanding, care, and support for individuals who are either sick or at risk of developing a disease. It is the view of the Science Council that:

- Genetic technologies and services are, and should continue to be, evaluated and delivered in the context of a caring society. Individual choice (autonomy), counselling, informed consent, and confidentiality are the cornerstones of the ethical delivery of genetic services.

Autonomy, counselling, informed consent, and confidentiality are the cornerstones of ethical delivery of genetic services.

- The primary objective of genetic applications in health care is to treat or prevent genetic disorders; the technologies should not be used with the primary goal of reducing the costs of health care or improving the human species. Genetic services should be initiated only if there are benefits to the recipient such as disease prevention or treatment, or lifestyle or reproductive choices.

- Individuals and families should have access to beneficial technologies in order to make informed decisions about their own health care and reproductive options. The decisions should be based on reliable technical information and accurate, non-directive counselling.

Individuals and families should have access to beneficial technologies.

- Participation in genetic services should be a matter of free choice. Individual and family decisions must be respected and supported. Individuals should not be penalized (through reduced medical or social services, for example) for their reproductive or personal health care decisions.

- Genetic technologies should be used in a manner consistent with acceptance of human diversity and disability. We must ensure that availability of genetic services does not decrease our acceptance of the disabled.

The availability of genetic services must not decrease our acceptance of human diversity and disability.

An Economic Context

Canada has a national health insurance that reflects fundamental social values. Our health care system* is not perfect, but it is probably as good as any in the world. It is a good compromise of quality, affordability, equity, and humanity.[16] But rising health care costs are increasingly stressing this balance.

Rising health care costs have resulted in cost-containment measures.

The cost of health care in Canada in 1987 amounted to 9.0 per cent of our gross national product[17] and accounted for 25-35 per cent of government expenditures at the provincial level.[18] The rising cost of health care has resulted in cost-containment measures and increasing competition for existing resources. This is the health-economics environment facing proponents of genetic health services.

Cost concerns are preventing delivery of proven services.

It is not possible to predict what genetic technologies and health services will become available or whether, overall, they will save health care dollars. What is certain is that the improved understanding of the role of genes in health and disease is resulting in the development of some health care applications that offer effective and efficient use of health care dollars.[19] But lack of resources is hampering delivery of some cost-effective genetic services of proven health benefit. The funding limitations reflect both the competition for resources and the relatively low priority genetic programs are generally accorded by the medical profession, health administrators, and health ministries.

Failure to integrate effective new services into publicly funded health care compromises the objectives of our health care system.

The difficulty in obtaining funds for genetic health services exemplifies the problems inherent in integrating any new technology into health care systems and suggests there is a need to look at the larger issues surrounding delivery and funding of health care in Canada. Universal access to comprehensive, publicly funded health care is an important Canadian objective that reflects fundamental social values. Failure to include effective new services — such as some genetic services — into publicly funded health care compromises this objective, and might also foster the development of privately offered services. The result could be a two-tier health care system based on ability to pay. This would run counter to the objectives of the Canadian health care system and to the stated wishes of the Canadian public.

An effective health care system must remain flexible. As scientific knowledge advances and consumer needs change, policy makers must continually reorder their priorities for health care delivery and ensure the incorporation of new knowledge and technologies.

An Educational Context

Better health education is required so that Canadians can make informed decisions about their health.

To better realize the benefits of genetic knowledge and technologies, and to avoid their misuse, the Canadian public, health care professionals, and health policy makers must become more aware of the current contributions and future potential of genetics in both preventing and treating disease. Education is key, and should begin in the elementary schools and be carried on through our secondary schools, universities, and training programs for health care professionals. But education is a life-long process and must also reach those in

* The 12 provincial and territorial health care systems, which reflect the principles of the Canada Health Act, are here collectively considered to be the Canadian health care "system."

the general public and health care community who have already completed their formal schooling.

At present, the majority of students in elementary and secondary schools receive little instruction in genetics. To reach all students, the role genes play in health and disease should be taught in elementary school and be part of the core curriculum in junior high school. Students should be introduced to both the health applications of genetic knowledge and the related social and ethical issues.

Even the providers of health care are not receiving an adequate education in genetics.[20] For example, genetics needs to be better integrated into the education of physicians at the undergraduate, postgraduate, and continuing education levels and should be taught in three different ways: as a basic science underlying all aspects of health and health care, as a specific course on medical genetics, and as an integral component of all other courses.

Genetics should be better incorporated into the education of health care providers.

An understanding of genetic predisposition to disease is also important in other health care fields, including dentistry, dietetics, nursing, pharmacy, rehabilitation therapy, and social work. At present, genetics is not well incorporated into the education and practice of any of these disciplines.

Finally, in a democratic society, an informed public is essential for individuals to make informed personal decisions and participate effectively in public policy making. To this end, Canadians need information that will improve their understanding of genetic health care technologies and services in particular, and the Canadian health care system in general.

Research Required

The research required to understand the role of genes and to develop health care applications is formidable and is likely to be a focus of national and international activity for a long time to come. Canadians are involved in genetics research not only to advance a body of knowledge with important health implications, but also to address specific mutations and diseases that are common, or cluster, in Canadian populations, and to foster the development of Canada's biotechnology sector.

As well as contributing to the growing knowledge base, Canadian research is developing solutions to health problems that cluster in Canadian populations.

Canada has proven expertise in certain areas of genetics research and Canadian researchers are at the forefront in the investigation of genetic diseases such as Duchenne muscular dystrophy, cystic fibrosis, and hypercholesterolaemia. Canadian research is contributing to the growing international information base on genes and their role in health and disease. The Canadian government recently recognized the importance of genetics research and researchers by establishing a genetics research network in the National Networks of Centres of Excellence Program.

Canadian researchers are at the forefront of several genetic diseases.

In addition, more research is required to develop solutions to specific Canadian health problems. As a consequence of immigration and settlement patterns, Canadian populations have their own specific mutations and diseases. The integration of genetic knowledge and technologies into population health studies is enabling researchers to identify particular genes and risk factors associated with these diseases and to begin to find ways of anticipating and preventing them.

Genetics research also provides opportunities for Canada's biotechnology industry.

Genetics research also provides opportunities for Canada's biotechnology industry. There is currently little private sector activity in this area: a Science Council survey conducted in 1989 identified fewer than 10 firms active in development of specific gene-disease diagnostics or therapeutics. Mechanisms to enhance the level of private sector research include tax credits for investors, increased direct funding, tax credits for biotechnology firms, and better patent protection.

In spite of the opportunities, medical research in Canada is chronically underfunded compared to other developed countries, and the proportion of research funds spent on genetics research is relatively small.[21] Lack of resources is hampering progress in resolving important health problems.

The Need for Action: Goals and Initiatives

Canada's health care systems are not adequately delivering services based on existing genetic knowledge and technologies.

Canada's health care systems are not adequately delivering services based on existing genetic knowledge and technologies. Nor is our increasing understanding of the role of genes in health and disease being considered in health care planning. Existing genetic technologies and related services that are beneficial and cost effective should be better integrated into the publicly funded health care systems; new technologies and health services should be phased in as appropriate, based on evaluations of health benefits, health risks, and costs. We should proceed with the development of genetic technologies and the delivery of genetic health services, but with caution.

It is important to recognize that along with the health benefits associated with genetic technologies there is the potential for harm due to their misuse. The technical and ethical implications of genetic technologies and services must be carefully considered. Ethical considerations are critical to planning and decision making in all aspects of medical genetics including research, technology development, service delivery, and use of information. Genetic technologies and knowledge must be applied in the context of a caring society: a society that supports individual choice as well as advancement of knowledge.

Planning and action are required of policy makers, health care professionals, educators, and consumers.

To ensure effective and ethical development and delivery of genetic technologies and services, planning and action are needed now by health policy makers, health care providers and administrators, educators, and the public. To address this need, the Science Council has identified nine goals and recommends two initiatives.

Goals

Nine goals should guide future policies.

The Science Council believes that the following goals should guide future policies on genetic information and technologies. Together, they provide the basis for using genetic knowledge within an ethical and social framework that will reinforce Canada's health care values and contribute to improved health care delivery.

1. To improve delivery, within Canadian health care systems, of appropriately evaluated diagnostic, preventive, treatment, and counselling services based on existing genetic knowledge and technologies.

2. To continue to integrate new, beneficial genetic technologies and services into Canadian health care systems.

3. To ensure that any person with or susceptible to genetic disease, or at risk of having children affected by genetic disease, has equitable access to genetic health services within Canadian health care systems. The decision to use genetic services should remain with the individual.

4. To assess the safety and effectiveness of new genetic technologies. Assessments should encompass ethical, economic, and technical considerations.

5. To support more research on genetic factors in the origin, development, and effects of disease, and on the prevention and treatment of genetic disease.

6. To ensure that appropriate regulatory mechanisms and guidelines are in place and implemented for genetics-related research and health care, and for use of genetic health information.

7. To better incorporate genetics into the education and re-education of health care providers and into the examinations for graduation, licensing, and specialization.

8. To increase public awareness and understanding of human genetic diversity, genetic susceptibility to disease, and related social issues through improved science and health education in the schools and through public education programs.

9. To improve health information, data management, record linkage, and disease classification systems to accommodate genetic issues.

Initiatives

To meet the identified goals, the Science Council recommends that:

Two mechanisms are urgently needed to assist in the timely and efficient delivery of genetic services, and to address the full range of technical and ethical issues.

1. All provincial health ministries have in place committees mandated to advise on timely and efficient delivery of genetic services.

2. The federal and provincial health ministries establish a joint committee on genetic services and information to address the full range of technical and ethical issues associated with current and emerging genetic technologies and their applications. This committee should be multidisciplinary and represent the users of health care, as well as the planners and providers.

2. THE ROLE OF GENES IN HEALTH AND DISEASE

Canadians are leading longer lives than ever before. Many of the diseases that were devastating to previous generations are no longer a major threat. One hundred years ago tuberculosis and pneumonia were the leading causes of death, and the infectious diseases of childhood made reaching puberty a highly uncertain proposition.[22] Today, tuberculosis and many of the formerly lethal ailments of childhood are largely under control, at least in the developed world. Even though viral diseases, including the common cold, remain a health problem requiring attention, their contribution to mortality in Canada is low. Infectious diseases, with the conspicuous exception of acquired immune deficiency syndrome (AIDS), have largely been tamed through effective public health measures.

The common diseases of today are different from the diseases of 100 years ago.

The major Canadian health problems now include diseases of the heart and circulatory system, cancer, and the common chronic diseases of middle and old age.[23] Effective strategies to deal with these problems are not yet available.

Heart and circulatory diseases, cancer, and the diseases of old age now predominate.

Before the middle of the 19th century doctors could set bones, lance boils, alleviate symptoms, and offer comfort; what they could not do very often was cure disease. Social changes, public health measures, vaccines, and new medical technologies, including surgical and pharmaceutical interventions, have all been responsible for the increasing average life expectancy and reduced mortality of Canadians. Controls on workplace contaminants and some reduction of environmental pollutants have also led to improvements in health.

Social changes, public health measures, and new medical technologies have increased life expectancy.

However, despite tangible successes, modern medicine is still limited in its capabilities. Although medical advances and more effective drugs and operations appear continually, we have reached what seems to be a plateau in health status. The ability to prevent and treat disease remains limited in part by lack of understanding of the underlying cause and processes of most diseases, and scarcity of the tools to predict, diagnose, and treat them. The emerging information on genes and their role in health and disease is helping to provide such tools.

Modern medicine is still limited in its capabilities, but understanding the role of genes in health and disease is providing new tools.

Achieving Health

Most current definitions of health involve more than the absence of disease, although that remains the core component of the concept of good health. Accordingly, much of our health care effort is directed toward identifying and dealing with any deviations from the balance that constitutes good health. The causes of such deviations may be external (such as infection or injury) or internal and innate to the biology of the individual (such as the genes for Tay-Sachs disease or cystic fibrosis, classic metabolic disorders). It is becoming apparent that most diseases are multifactorial: they result from a combination of internal and external factors.[24] Their occurrence reflects both the predisposition of the individual to the specific disease, and the external environmental factors that may stimulate onset of the disease. The patient is not simply the host of a specific disease, but an individual with complex, interrelated requirements that must be met to maintain health. Understanding the causes of a disease is key to developing ways to prevent or delay onset, or to treat the disease when prevention is not possible.

Most diseases are multifactorial — they result from a combination of internal and external factors.

Box 2
Examples of Single-Gene Disorders: Frequency and Severity

Adult Polycystic Kidney Disease (APKD)
One in every 1000 newborns will eventually develop APKD.

The early signs of the disease include pain, blood in the urine, frequent kidney infections, and high blood pressure. The average age at onset of the disease is 41 years. Between 5 and 10 per cent of people with APKD develop end-stage renal disease. APKD is now a major reason for renal dialysis. Enlargements (aneurysms) of the cerebral arteries are found in 10 to 30 per cent of cases. About 3 per cent of people who die from ruptured cerebral aneurysms have APKD.

Cystic Fibrosis (CF)
About one in 2000 Caucasian newborns develops CF. Approximately one in 20 Caucasians carries a copy of the gene that causes CF if present in a double dose.

CF affects the glands that secrete tears, sweat, saliva, and mucus. Excess production of sticky mucus in the lungs makes breathing difficult and results in progressive lung and heart damage. The lungs of a person with CF are an ideal environment for infections to develop. The abnormal mucus level prevents adequate flow of pancreatic enzymes, limiting the effectiveness of the digestive system. The severity of these symptoms varies considerably. Treatment of CF symptoms has improved significantly in recent years. Approximately 50 per cent of people with this illness now survive to about 24 years of age. In the 1960s the 50 per cent survival rate occurred at age four.

Canadian geneticists identified the CF gene in 1989. There are a number of different forms of the gene that can result in CF. At present, about 70 per cent of persons carrying a mutant CF gene can be identified.

Duchenne Muscular Dystrophy (DMD)
About one in every 3500 males is born with the gene that causes DMD. The disease is extremely rare in females.

The disease is characterized by progressive and eventually fatal muscular weakness and wasting. The symptoms usually begin before the age of five. Death due to respiratory infection or heart failure usually occurs by the third decade of life.

Familial Hypercholesterolaemia (FH)
One in every 500 people in North America has one copy of the gene that causes FH. One in a million newborns has two copies of the gene. The incidence is two times higher in French Canadian populations.

FH affects cholesterol levels. People with two copies of the gene have extremely high blood cholesterol levels, which usually induce death from coronary heart disease by the age of 30. People with one copy of the FH gene also have abnormally high cholesterol levels. About 50 per cent of men with one copy of the gene have symptoms of coronary heart disease by 50 years of age. The corresponding proportion for women is about 33 per cent.

Haemochromatosis
About 10 per cent of the Canadian population carries one copy of the gene that causes the disease when present in a double dose. Carriers may have some symptoms. Two to three people in every 1000 have haemochromatosis.

The gene for haemochromatosis causes excessive and damaging accumulation of iron in organs such as the liver, heart, and pancreas. Iron accumulation can produce enlargement of the liver, diabetes, and heart disease. If left untreated, haemochromatosis can be fatal.

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It is now generally accepted that human health is dependent on the interaction of four major factors in what a milestone Canadian report called the "health field concept."[25] The factors are: human biology, the external environment, lifestyle, and health care organization. It makes sense that all four elements must be continually addressed in an integrated and balanced manner if we are to achieve a healthy population. However, there will be instances when one or another of these factors will offer a particular opportunity to address specific health problems or improve general health status. The growing knowledge of the role of genes in health and disease is providing such an opportunity now.[26]

Human health is dependent on four factors: human biology, external environment, lifestyle, and health care.

Genetic Disease

The general public, most patients, and many health care professionals tend to think of genetic disease as the relatively rare, single-gene diseases such as haemophilia, Huntington disease, or cystic fibrosis (see Box 2). However, the impact that genetic make-up has on health is much more far-reaching. Genes, by virtue of their essential role in the structure and function of cells, are probably implicated in most diseases.

The effects of genetic make-up on health are far-reaching, but still only partly understood.

Each individual has a unique genetic inheritance. For most disorders, the links between that inheritance and the occurrence of disease are complex and still incompletely understood. However, the technology to characterize or "see" genes is being refined and is resulting in a growing understanding of the role of genes in health and disease. Information implicating genes in specific diseases is emerging at an accelerating rate. To date, nearly 5000 disorders and traits with classic inheritance patterns have been identified, and their number continues to grow (see Box 3).

Nearly 5000 disorders and traits with classic inheritance patterns have been identified.

It is now clear that genes play an important role, as predisposing agents, in a much wider spectrum of diseases than originally suspected. The influence of genes is recognized in such common serious disorders as hypertension, many forms of cancer, psychiatric disorders, and circulatory and heart disease.[27] Information on the occurrence and current understanding of the role of genes in some common diseases is provided in Boxes 4 and 5. Genes are also implicated in many diseases not traditionally thought of as genetic, including infectious diseases[28] such as tuberculosis and polio (see Box 6). Infectious diseases must have a susceptible host, and genes are one of the factors influencing susceptibility.

Genes also play an important role, as predisposing agents, in a wide spectrum of diseases.

As primarily nongenetic diseases are better controlled through public health, social policies, and medical technologies, the proportion of gene-related disease is growing.[29] Polio is an example of an infectious disease controlled in Canada through immunization programs and better sanitation; as a result, genetic forms of chronic musculo-skeletal disability have become more prominent.[30] Rickets is an example of a disease in which the genetic causes became more significant when the other contributing causes were controlled (see Box 7).[31]

The relative significance of disorders with genetic causes is increasing.

The concept of genetic predisposition to disease is not new. In 1931 Sir Archibald Garrod brought this already old issue to the attention of his medical contemporaries in his book *Inborn Factors of Disease*.[32] Garrod was ahead of his time and the significance of the concept was not widely accepted. The medical community of the day was preoccupied with more immediate health problems; infectious diseases such as diphtheria, polio, and tuberculosis had not

The concept of genetic disease is not new, but most of the diagnostic technologies are.

Box 2 (continued)

Haemophilia A and Von Willebrand Disease

Usually only males develop haemophilia A. The disease affects one in every 10 000 newborn males. Von Willebrand disease affects as many as one in 200 people (male and female).

Both haemophilia A and Von Willebrand disease result from a deficiency in factor VIII, a substance involved in blood clotting. The basic feature underlying both diseases is the tendency to bleed. The symptoms of the two conditions vary considerably in severity. Mild cases of both diseases involve excessive bleeding only in response to serious trauma such as surgery. In severe cases of haemophilia A, bleeding in the joints without any external cause may start by six months of age. The average life span of someone with haemophilia A is about 40 years.

Huntington Disease

One in every 10 000 Caucasians has Huntington disease. For every person with the disease, there are an average of five to eight relatives at risk. Usually the disease is transmitted to offspring before it is diagnosed in the parent.

The disease involves degeneration of a specific region of the brain. This produces symptoms that include movement disorder, intellectual dysfunction, and personality changes. Huntington disease is progressive and eventually fatal, usually 15 to 20 years after onset. In most cases its symptoms begin to appear between 30 and 45 years of age.

Persons inheriting the gene from their father tend to experience earlier onset of the disease than those inheriting it from their mother.

Sickle Cell Anaemia

This disease occurs most often in black populations.

Two copies of the gene result in sickle cell anaemia, which can be fatal. The disease produces an abnormal form of haemoglobin which interferes with blood circulation. Individuals with only one copy of the gene are carriers and may themselves show mild symptoms of the disease.

People who have only one copy of the gene are resistant to falciparum malaria infection. This resistance is a "selective advantage" and has favoured maintenance of the sickle cell gene in the population. Among U.S. blacks, one in every 625 newborns has sickle cell anaemia and 8 per cent are carriers. In some areas of Africa carrier frequency is up to 30 per cent because of the protection against falciparum malaria. With improved public health measures and medicine to prevent and treat malaria, the advantage of the sickle cell gene is declining in importance.

yet yielded to public health solutions. Moreover, the diagnostic technologies that would identify individuals genetically predisposed to disease had not yet been developed. Today, appropriate diagnostic tests are increasingly available.

Occurrence of Genetic Disease

Common diseases with a genetic component affect many Canadians. In addition, there are more than 3600 known single-gene diseases that collectively affect a significant number of individuals even though each is relatively rare. Since genetic diseases are often characterized by early onset,[33] the resulting years of ill health, the years of life lost, and the subsequent social, emotional, and financial costs are high.[34] The costs of one disease — cystic fibrosis — are outlined in Box 8.

Diseases with a genetic component affect many Canadians.

At present, we cannot quantify the contribution of genetic disease to sickness and death in Canada. For many diseases an understanding of the role of genes is only now emerging. To understand the importance of genetics in the health and sickness of Canadians will require better knowledge of the causes of disease, more emphasis on genetic epidemiology, and better methods of classifying disease and processing health data. Available figures tend to underestimate the occurrence of genetic disease. Nevertheless, existing estimates show that genetic disease significantly contributes to disease and affects the quality of life and health. It is estimated that during their lifetime 60 per cent of the population will experience a disease that in some cases has a genetic component to its cause.[35] Genes are implicated in health status and in disease at all stages of life.

Current figures underestimate the occurrence of genetic disease during the course of life.

Some 60 per cent of the population will experience a disease with a genetic component to its cause.

From Conception to Birth

More than half the pregnancies of healthy women fail to produce liveborn babies.[36] Genetic aberrations are a major factor in failed pregnancies, particularly those occurring during the first three months after conception. Chromosomal abnormalities are detected in 50 per cent to 60 per cent of early, recognizable spontaneous abortions.[37]

Genetic aberrations are a major factor in failed pregnancies.

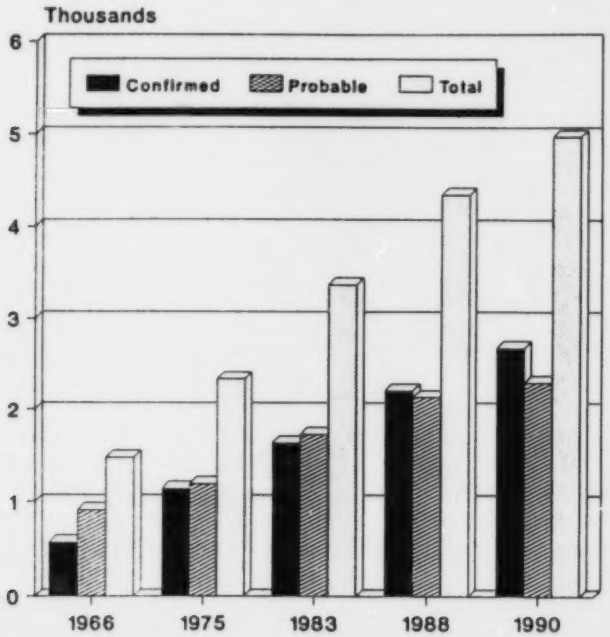
From Infancy to Young Adulthood

Data from the British Columbia Health Surveillance Registry show that at least 5.3 per cent of the province's population under 25 years of age has a handicapping condition that is wholly or partly genetic (see Box 9). The specific handicapping conditions differ in severity but all affect the quality of life and call for health care services.

Available data show that disorders with a genetic cause are common in infancy and young adulthood.

Mortality rates and hospital utilization statistics also provide a partial indication of the relative significance of genetic factors. In Canada and the United States at the turn of the century, the infant mortality rate was approximately 150 per 1000 live births, with 5 deaths per 1000 due to clearly genetic causes. Today the infant mortality rate is only a tenth of what it was in 1900, but the number of infant deaths related to genetic causes has remained constant at about 5 per 1000 live births.[38]

Box 3
Number of Disorders and Traits Associated with Specific Mutations



Box 4
Examples of the Genetic Contribution to Multifactorial Disease

Multifactorial disease results from a complex interaction of genetic and environmental influences. We are just beginning to understand the ways in which genes contribute to multifactorial disease. In many cases the sequence of events that initiates, promotes, and triggers the symptoms of disease has not yet been identified.

Alzheimer Disease (AD)
Two to three per cent of Canadians over 60 years of age have AD. The proportion increases to about 20 per cent in people over 80. The disease progresses from forgetfulness to complete inability to care for oneself. It is estimated that AD contributes to the death of at least 10 000 Canadians every year.

The proportion of cases of AD with a genetic basis has not been established but estimates range from 10 to 100 per cent. In some families the disease is inherited as an autosomal dominant (see Box 10). Genetic markers for familial AD have been identified on chromosome 21 but the gene thought to produce AD has not yet been identified. Other genetic and environmental factors probably modify the gene's impact, for instance by influencing the age at which symptoms of the disease appear.

Coronary Heart Disease (CHD)
The death rate in 1987 from heart disease (208.5 per 100 000 population) was greater than from all cancers (175.5 per 100 000 population). Heart disease is also a major cause of premature death, accounting for 17.2 per cent of all potential years of life lost in 1985.

A family history of CHD occurring by 55 years of age is the strongest risk factor for CHD. Several other risk factors with genetic involvement have also been identified, including high cholesterol levels, high blood pressure, and diabetes.

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Up to 50 per cent of children in Canadian paediatric hospitals have disorders that are known to be strongly influenced by genetic factors.[39] For example, 57 per cent of childhood cases of musculo-skeletal disease admitted to hospitals are gene-related.[40]

In Adulthood

Our knowledge about the effects of genetic factors on the health of individuals beyond 25 years of age is limited. There are, however, indications that genes play a significant role. In the 1970s, it was estimated that 12.5 per cent of hospitalized adults had genetically influenced disorders.[41] Data indicate that of individuals considered severely mentally retarded, approximately 15 per cent have disorders that are inherited through a single gene and 45 per cent have disorders that are in some way genetically influenced.[42]

Genes also play a significant role in the health of adults.

Genetic Material, Variation, and Mutation

The phenomenon of heredity — the transmittal of characteristics from one generation to the next — has been recognized for hundreds of years. However, the genetic mechanisms of heredity are only now being clarified. We now realize that genes we inherit from our ancestors control many of the processes essential to normal biological function and health.

Genes control many of the processes essential to normal biological functions and health.

Genetic material serves as an internal blueprint for the detailed function of the human body. The genetic information is carried on molecules of deoxyribonucleic acid (DNA) found in all cells. (Appendix 1 provides basic information on DNA, genes, and chromosomes.) Information is currently accumulating almost daily on human DNA sequences, the biological processes they encode, and the diseases they cause (or inhibit).

Information is accumulating rapidly on DNA sequences, the processes they encode, and related diseases.

An important feature of genes is their ability to be reproduced identically and transmitted from generation to generation. But genes can also be altered: the specific sequences of nucleotides along a DNA molecule are susceptible to change through a process known as mutation. Mutations can happen in a number of ways:[43]

- through rearrangement of genetic material (DNA strands) during the process of cell division to produce eggs or sperm;
- through exposure to specific environmental factors (called mutagens);
- through a failure of the DNA repair mechanism; or
- as a consequence of spontaneous change.

The process of mutation results in genetic variation, which enables species to adapt to changing conditions. However, what is good for the survival of the species is not always healthy for the individual. In most cases, a random change in a complex, specialized DNA sequence will not be advantageous to the individual organism.

The process of mutation results in genetic variation. Although mutations fuel evolution, they usually impair health.

Because of the combination of genetic inheritance and new mutations, each of us has a susceptibility or resistance to various diseases. An understanding of genetic variability helps to explain why only certain individuals develop specific diseases, and why those diseases vary in their severity and prognosis among individuals.

Box 4 (continued)

The cholesterol levels of genetically related individuals tend to be more similar than the levels of unrelated individuals sharing the same household. Between 2 per cent and 4 per cent of the population has a known single-gene disorder (familial hypercholesterolaemia) that leads to CHD. There is also a genetic trait (hyperalphalipoproteinaemia) that appears to protect against CHD.

Blood pressure levels of family members also tend to be more alike than those of genetically unrelated individuals sharing the same household. One-quarter of all people with hypertension (high blood pressure) are under 60 years of age and also have one or more siblings with the same condition. Many from this group also have lipid abnormalities (e.g., abnormal cholesterol levels).

CHD often affects people with diabetes mellitus. There are many different types of diabetes, and there is evidence for genetic involvement in many of them.

There are other genetic conditions that contribute to the overall incidence of CHD. For example, homocystinuria is a relatively uncommon recessively inherited disorder. However, between 0.5 and 1.4 per cent of the population carries one copy of the gene that causes the disease when present in a double dose. People with one copy of the gene have a much greater chance than average of early onset of arterial disease.

Lung Cancer

In 1989 about 11 700 Canadian men were diagnosed as having lung cancer. The corresponding number for women was 5100. The total number of deaths from lung cancer in that year was approximately 13 500. This disease is also a leading cause of premature death: it accounted for 32 per cent of all potential years of life lost to cancer in 1986. Damage to chromosome 3 has been associated with all the major forms of lung cancer. In some cases this damage may involve an inherited component. Lung cancer is more common in some families than others, even when smoking is taken into account. Smoking is more likely to cause lung cancer when there is a family history of the disease. A genetically influenced biochemical response to cigarette smoke has been identified that is associated with 20 to 40 times the average risk of one type of lung cancer. About 10 per cent of the population shows this particular response.

Schizophrenia

The risk of having schizophrenia at some time during one's life is about 1 per cent. More than 40 per cent of all days spent in Canadian psychiatric hospitals are due to schizophrenia. There are many different types of this disease. Symptoms may include hallucinations, disordered thought, delusions, and disorganized behaviour.

The risk of developing schizophrenia varies with the closeness of one's genetic relationship to a person with the disease and the number of affected people in the family. For example, the brother or sister of a schizophrenic has between a 40 per cent and 60 per cent chance of developing schizophrenia if both parents are also affected. This risk falls to about 15 per cent if one parent is affected and to 10 per cent if neither parent is affected. If one member of a pair of identical twins is schizophrenic, there is a 55 per cent chance the other twin will also develop the disease. In non-identical twins of the same sex the risk is about 18 per cent.

Evidence for genetic involvement in schizophrenia also comes from studies of adopted children. Individuals adopted early in life share genetic characteristics with their biological parents but share environmental experiences with their adoptive parents. Adoptees are about three times more likely to develop schizophrenia if their biological parents have the disease than if their adoptive parents are affected.

Schizophrenia may in some (but not all) cases be associated with a particular region of chromosome 5. Studies indicate that there may be different genes involved in different families.

The effect of mutations on the organism can range from the insignificant to the catastrophic. If the variation in a specific nucleotide sequence results in the failure of the gene to perform its functions successfully, the consequence can be disease, malformation, or death.[44]

The effect of mutations may range from the insignificant to the catastrophic.

Some genetic disorders are inherited, resulting from mutations in DNA passed on from parents. Other genetic disease results from mutations in the body cells of an individual; the resulting disorder may or may not be transmitted to offspring. There are several ways in which mutant genes can be involved in the cause of disease (see Box 10). The presence of a specific mutant gene can result in the development of a specific disease. For example, the presence of a Tay-Sachs mutation leads invariably to onset of the disease, with death occurring in childhood. In other disorders, the presence of the mutated gene alone is not enough to cause manifestation of the disease; other biological factors or environmental factors are also required. These are multifactorial diseases. In such cases the genes only make the individual susceptible to the disease. Polygenic diseases, a category of multifactorial disease, require more than one mutant gene to start the pathological process.

Mutant genes may be involved in disease in a number of ways...

...in some cases a specific gene results in a specific disease; in other cases a gene may confer only susceptibility.

The same clinical manifestations (symptoms) can result from a variety of causes. For example, over 50 different mutations can cause the hereditary anaemia called ß-thalassaemia.[45] Several different mutations, all in the same gene, have also been linked to familial hypercholesterolaemia.[46] Knowledge of the specific mutation has implications for diagnosis and for treatment of the related disease.

Improved knowledge of genes and their relationship to disease will help answer the following questions:

- Are mutations an important underlying cause of the disease?
- Which mutations result in disease or susceptibility to disease?
- What causes the mutation and can it be prevented?
- What are the cellular and molecular effects of the mutation?
- How does a mutation produce the clinical signs and symptoms of a disease?
- Do different mutations cause the same clinical manifestation?
- Does the mutation always result in the disease?
- What other factors are required for onset of the disease?
- Is there a delay between the occurrence of a mutation in an individual and the clinical expression of the resulting disease?
- Is diagnosis of the defect possible before the onset of the clinical signs of the disease?

Our accumulating genetic knowledge will help answer many questions about the cause and development of disease.

A number of methods exist to identify disease-mutation links. The methods are based on the study of natural variation in DNA sequences and the association between specific DNA sequences and clinical disorders.[47] Recombinant DNA technologies provided the technical breakthrough that allows the isolation and analysis of genes, and enables the search for the genetic basis of disease to occur directly at the DNA level. The technologies involve taking samples of the complete DNA complement of an individual from accessible tissues, and breaking the DNA molecules down into smaller, more manageable fragments.

Recombinant DNA technologies enable the search for the genetic basis of disease to occur directly at the DNA level.

Box 5
Cancer:
A Genetic Disease

Cancer results from changes in genetic material that produce abnormal, accelerated cell growth. The processes that produce cancer are varied and complex. Most cancers are the result of interaction between an individual's genetic make-up and the environment. Cancer-causing genetic changes fall into two broad classes.

- Some cancers result from mutations that involve loss of specific chromosomal regions. Loss or inactivation of genes that have an "anti-cancer" function can begin the cancer process.
- Mutations can also induce particular genes to gain cancer-causing abilities. Prior to mutation, these genes are called proto-oncogenes and are thought to play a role in regulation of cell growth. Once a specific genetic alteration has occurred, proto-oncogenes are converted to oncogene status and uncontrolled cell growth follows.

Different groups in society have different risks of developing cancer. There will always be some cases of cancer because genetic material mutates spontaneously. People who are exposed to agents that induce mutation (e.g., certain viruses and chemicals, radiation) have a higher risk than people who are not similarly exposed. An estimated 20 per cent of cancer cases involve DNA viruses; these cases may be avoidable using vaccines against the infecting viruses.

Some individuals possess characteristics that favour spontaneous or induced mutations. For example, people who have a defective DNA repair surveillance and repair system (which corrects spontaneous or induced mutations in the normal situation) are at higher than average risk for cancer.

Another risk category includes people with an inherited susceptibility to particular cancers. A number of events have to occur before a malignant tumour is produced. People born with a susceptibility are already at stage one of the process. If the other necessary events occur, which may include environmental exposure, such people will develop cancer.

For example, retinoblastoma affects one in 14 000 newborns and is usually manifest in children by the age of seven. Retinoblastoma produces tumours that may necessitate eye removal unless detected very early. The disease can be inherited or occur in a family with no previous history of the disease. Those with a predisposition to retinoblastoma inherit a specific mutation at conception from one of their parents. The mutation is present on one of the two copies of chromosome 13. Retinoblastoma develops if a similar mutation is acquired on the other copy of chromosome 13. Cases occurring in families with no previous history of the disease follow a similar route except both mutations must be acquired. The basic genetic alteration is thought to be the same in both inherited and non-inherited cases.

Evidence is emerging that genetic predisposition may be involved in a significant proportion of cases of the more common cancers. For example, more than 50 per cent of cases of colon cancer may involve genetic susceptibility and about 9 per cent of breast cancer cases are associated with a particular inherited genetic mutation.

A better understanding of inherited cancers will help in unscrambling the contributions of genes and the environment to common cancers, and increase the chances of intervening effectively at the most appropriate time. Possibilities for more effective preventive and therapeutic interventions include a more accurate assault on cancer-causing environmental hazards; avoidance (particularly by genetically susceptible people) of cancer-causing agents that cannot feasibly be eliminated from the environment; and application of therapies that replace or mimic the effects of "anti-cancer" genes.

The technologies can be used to identify whether a gene with a known gene product is responsible for a specific disease; to locate and identify genes responsible for single-gene disorders, but whose function is still unknown; and also to identify genes responsible for multifactorial disorders. (Some basic information on recombinant DNA technologies and their applications is provided in Appendix 2.)

Disease-mutation links can be identified by studying natural variation in DNA sequences, and correlating specific sequences with disorders.

The most direct approach to identifying a disease-causing mutation is to compare the nucleotide sequence of genes between affected and normal individuals. However, due to the sheer size of the human genetic complement or genome, this is not practical unless the location of the relevant DNA sequence is known. One successful approach to help focus on specific disease-causing mutations involves comparing specific landmark sequences within the total complement of DNA. These sequences are chosen because they are known to vary, to exist in different forms called alleles. By studying allelic differences between healthy individuals and individuals with a specific disease, it is possible to link many major genetic diseases to specific alleles. The discovery of such links then helps to focus the search for the specific mutation causing the disease. The cystic fibrosis gene was discovered in this way.

The concept that certain individuals are at particular risk for, or susceptible to, disease because of their genetic make-up underlies the new and growing field of genetic epidemiology, and helps to explain why some diseases cluster in families, ethnic groups, or geographical areas. For any specific clustering of disease, genetic epidemiology helps to determine the role of common environmental exposure, biologically inherited susceptibility, and culturally inherited risk factors such as behaviour or lifestyle.[48]

Twin and adoption studies are clarifying the relative contributions of genes and environment to certain diseases.

Twin and adoption studies are clarifying the relative contributions of genes and environment to certain diseases. Individuals adopted early in life share genetic characteristics with their biological parents but share environmental experiences with their adoptive parents. Such people offer insight into genetic and environmental influences on health and disease.[49] For example:

- Premature death: Genetic factors are significant contributors to premature, non-violent deaths. However, the relative importance of genetic and environmental factors appears to vary with the disorder.[50]

- Alcoholism: There is a substantial genetic component to alcoholism in some individuals. The frequency of alcoholism among adopted children of alcoholic biological parents is more than three times that of adoptees with non-alcoholic biological parents. Moreover, the frequency of alcoholism in the biological children of alcoholics is the same regardless of whether they are raised by their biological parents or adopted into another family.[51]

- Schizophrenia: The findings on schizophrenia are similar to those on alcoholism. The frequency of schizophrenia in the biological relatives of adopted schizophrenics is about three times the frequency in their adopted relatives. The biological children of schizophrenics have approximately the same chance of developing schizophrenia whether they are brought up by their biological or adoptive parents.[52]

Box 6
A Story the Brontë Sisters Didn't Tell Us

An old wives' tale says that tuberculosis runs in families. The conventional explanation is that the family member with active tuberculosis infects others in the family. The history of the Brontë family may tell another story: it takes two sets of genes to make an infection — the invader's and the host's.

The sisters, Emily, Charlotte, and Anne, are famous for their contribution to 19th century English literature. All died young, apparently of tuberculosis. Their mother died young too, some say of the same disease. The family — mother, father, three daughters, and one son — lived together in the parsonage at Haworth, Yorkshire. The father lived 84 years despite his heavy exposure to tuberculosis. The son died of something else.

A Canadian investigator (Emil Skamene) used an inbred mouse colony to discover a genetic factor in tuberculosis infection. A gene on mouse chromosome 1 confers resistance to tuberculosis infection; a variant of the gene confers susceptibility. Skamene then showed, by comparative gene mapping, that humans have a similar gene on chromosome 2.

Box 7
Rickets: An Example of the Increasing Significance of Genetic Cause

Rickets provides a good illustration of a disease where the genetic cause is becoming more significant as other causes are effectively prevented or treated. The history of rickets also shows how the most common route to disease can shift over time.

In the 19th and early 20th centuries rickets was common in industrialized Europe and the northern regions of North America. The principal cause was vitamin D deficiency as a result of poor diet and inadequate exposure to ultraviolet radiation. Following the discovery of vitamin D in the 1920s and the recognition of its dietary significance, food regulations were enacted to protect the population from dietary deficiencies. This led to a dramatic decline in the incidence of rickets. But rickets did not disappear entirely. Today patients still suffer from rickets, but it results from inherited disorders affecting their mineral metabolism rather than from a dietary deficiency. There are several different genetic causes of rickets; for each one, the specific metabolic problem must be identified and the treatment tailored appropriately.

Box 8
Cystic Fibrosis: An Example of the Costs of a Genetic Disease

Cystic fibrosis (CF) is enormously costly. Not all the costs are financial. The emotional and psychological impact of the disease is largely confined to those individuals who have CF themselves, and their immediate families. The financial burdens of CF are also extensive, and these are borne not only by the families directly affected, but also by the Canadian public at large.

Hospitalization
On average, people with CF are hospitalized for 10 days each year.
Cost: $20 million per year

Outpatient care
All CF patients attend outpatient clinics on a regular basis, where they are cared for by a multidisciplinary team of health professionals, including nurses, physicians, physiotherapists, and dieticians. Providing the necessary care costs approximately $4000 per patient annually.
Cost: $10 million per year

(continued on page 30)

Mapping and Sequencing

Work is under way, both in Canada and internationally, on mapping and sequencing of the human genome. The objectives are to provide a more detailed picture of DNA, and to investigate the role and function of genes and the DNA segments between genes. The resulting knowledge will also help to identify mutations associated with disease and susceptibility to disease.

Work is currently under way to map and sequence the human genome.

The purpose of mapping the human genome is to establish the precise position of the genes along the DNA molecule in relation to one another.[53] Physical maps show the geographic location of specific genes along the chromosomes. Linkage maps are based on correlating the relative positions of specific genes with the probability that they will be inherited together. It is reasonable to assume that the genes for traits that are almost always inherited together are located near each other and hence are likely to remain together during the natural process of DNA recombination.

Gene mapping establishes the precise position of genes along the DNA molecule.

Scientists hope to compile successively higher-resolution genetic linkage maps and complementary physical maps. Knowing the precise location of the genes along the DNA molecule is widely regarded as essential for modern medicine as we look toward the 21st century.[54]

On the other hand, there is considerable controversy over the relevance of sequencing the human genome. Sequencing establishes the precise order of base pairs and provides a far more detailed picture of the genome than mapping. Knowing the nucleotide sequences provides the needed reference to identify and understand variation in genes and the effects of that variation on health and disease. But the task of sequencing the estimated three billion base pairs that make up human DNA is formidable. It is expected that complete sequencing will require international cooperation and $200 million a year for at least 15 years.[55]

Sequencing establishes the precise order of base pairs.

Sequencing the entire genome is a lengthy and expensive process, but will help us understand the effects of genetic variation on health and disease.

A major point of debate is whether big sequencing projects should be delayed until improved sequencing and data-processing technology are available. A second issue is whether it is worthwhile to sequence the entire genome, or whether attention should focus first on stretches of DNA associated with protein production and stretches showing extensive variation associated with health and disease.[56]

Status of Knowledge

Our knowledge of genes, although increasing rapidly, is still limited. At present we do not know the exact number of genes in human DNA. Information is also incomplete on the precise role of specific genes and their products, the degree of genetic variability that exists in the population for each gene, specific mutations and their related disorders, and the factors that can trigger disease in genetically susceptible individuals. Of the estimated 50 000 to 100 000 human genes, only approximately 1600 have had their chromosomal location identified. Fewer than a quarter of these have had portions of their DNA sequenced, and the complete nucleotide sequence is known for fewer still.

Our knowledge of genes is still very limited.

Nevertheless, the information available on the genes that have been mapped and characterized, and on the distinctive DNA sequences (called markers) that

Box 8 (continued)

Drugs
The most commonly used drugs include antibiotics which combat or prevent lung infections, and aerosol solutions which thin and loosen mucus. The cost of all the drugs used to treat the disease averages $5000 per patient per year, but may reach as high as $10 000.
Cost: $12.5 million-$15 million per year

Equipment and nutritional support
Individuals with CF require regular home physiotherapy sessions involving equipment for percussion and postural drainage, and for inhalation therapy. The digestive dysfunction associated with the disease means that they also need vitamins and diet supplements.
Cost: $6 million per year

Lung transplantation
Transplantation is a comparatively new form of treatment for CF patients who are gravely ill. The number of procedures performed in Canada each year is expected to reach 30 or more in the near future. Each operation costs $150 000.
Cost: $4.5 million per year

Personal burdens
Individuals with CF and their families must cope, every day, with chronic illness and the prospect of early death. The disease may also compound the normal problems associated with adolescence, such as establishing independence and satisfying social relations. Although improved treatment of cystic fibrosis has resulted in a dramatic increase in life expectancy, people with CF face loss of personal and family income, loss of opportunity, and loss of a substantial portion of potential working life.
Cost: inestimable

Box 9
Frequencies of Genetic Disorders in Children and Young Adults in British Columbia (1952-83)

Category of Genetic Disorder*	Rate per Million Live Births	% of Total Births
Dominant	1395.4	0.14
Recessive	1665.3	0.17
X-linked	532.4	0.05
Chromosomal	1845.4	0.18
Multifactorial	46 426.2	4.64
Genetic, but unknown mode of inheritance	1164.2	1.16
TOTAL	53 018.9	5.3**

* For an explanation of the categories of genetic disorder, see Box 10.
** Figures do not sum due to rounding.

also allow genes to be traced in families, is a powerful tool with applications in the identification, counselling, and treatment of individuals at risk for specific genetic diseases.

Limitations in Canadian Health Data

Canadian health data cannot be used to document reliably the contribution of genetic disease to death and disability, because the existing statistics do not allow for identification of the particular cause of the disease. To determine the role of genetics in the health and diseases of Canadians will require better knowledge of the causes of disease, more emphasis on genetic epidemiology, and better methods of classifying disease and processing health data.

Determining the role of genetics in the health of Canadians will require better methods of classifying disease and processing health data.

The system currently used in Canada for classifying disease is the internationally accepted International Classification of Disease, Ninth Version (ICD-9).[57] The ICD-9 is generally not useful for indicating cause of disease. The Canadian representatives to the international committee responsible for amending the ICD system have called for modifications, including specification of cause of disease. In the interim, development and use of common, cause-related subcodes by Canadian genetic centres would expand the pool of comparable data.

The linking of health records — bringing together health data for individuals and families to form a composite record — can clarify the distribution of disease within the population and the cause and progression of disease. Most provinces are now moving toward health record linkage because it provides better health statistics and related health care benefits. Unique identifier numbers are the most efficient way of achieving record linkage, but they have raised concerns regarding confidentiality and use of the data.[58] Nevertheless, protocols to protect confidentiality have been developed.

Health record linkage clarifies distribution, cause, and progression of disease; most provinces are working on ways to link health records.

In establishing record linkage systems it is important that:

- different provincial systems be compatible, to accommodate movement of individuals between provinces and record linkage for family members in different provinces;
- appropriate guidelines and protocol to ensure confidentiality accompany the use of record linkage and unique identifier numbers;
- individuals be made aware of the benefits of unique identifiers, and of how confidentiality can be maintained.

There is also a strong need for additional disease surveillance registries, similar to the British Columbia Health Surveillance Registry, to provide information on the nature, frequency, and cause of handicapping conditions. When registries are part of the health care delivery and planning system, they should incorporate protocols to protect the confidentiality of the individuals registered.

Disease surveillance registries contribute to health care delivery and planning; more registries are needed.

The B.C. Registry is an excellent model. It has been tracking health problems since 1952 and has evolved a simple system for coding diseases by cause, making it an especially useful database for genetic epidemiology.[59] The Registry has been used to improve the delivery of services to people with genetically influenced disease, to plan for disabled populations, as well as for

Box 10
Major Mechanisms for Genetic Diseases

Single-Gene Disorders

In single-gene disorders the presence of one specific gene variant can result in the disease. Single-gene disorders that are *autosomal dominant* require only one of the pair of genes to be affected for the disorder to be manifested; the other gene can be normal. (Examples: Huntington disease, Marfan syndrome.)

In single-gene disorders that are *autosomal recessive* both genes of the pair must be affected for the disorder to occur. If one gene is variant and one gene is normal the individual is not subject to the disease but as a carrier can pass the gene for the disorder on to subsequent generations. (Examples: cystic fibrosis, thalassaemia, sickle cell anaemia.) Possessing a single affected gene can confer health advantages or disadvantages. A single gene for sickle cell anaemia confers a resistance to falciparum malaria. A single gene for ataxia telangiectasia is associated with increased incidence of breast cancer.

In *sex-linked single-gene disorders* the occurrence and effects of the disorder differ between males and females. In females the sex chromosome pair consists of two similar chromosomes (XX), and the above rules for recessive and dominant expression of disease hold true. In males the sex chromosomes are not similar (XY), and as a consequence a normally recessive gene on the X or Y chromosome will not be balanced by another, possibly normal, gene. (Examples: Duchenne muscular dystrophy, haemophilia A.)

Multifactorial Disorders

A variety of factors are implicated in the expression of a *multifactorial disorder*. The requirements can include specific variations of a number of different genes occurring in conjunction, or exposure to specific environmental conditions such as radiation, diet, infectious disease, or social environment, or both. (Examples: congenital heart defects, cleft lip and palate.)

Chromosomal Disorders

Several disorders are due to *chromosomal* abnormalities. These disorders are generally not hereditary. (Example: Down syndrome.)

research purposes. As the population ages, the Registry will help identify the genetic components of the chronic diseases of middle age.

3. GENETIC TECHNOLOGIES AND HEALTH CARE APPLICATIONS

The goal of health care is to reduce the burden of disease on individuals and society. Existing and emerging health care technologies can be used to predict, diagnose, prevent, treat, or avoid genetic diseases. Well-established methods — based on inheritance patterns, diagnosis of symptoms, and interpretation of metabolite patterns — have been making a valuable contribution to health care in Canada for several decades. These methods will continue to play an important role.

New technologies have the potential to revolutionize health care, making it possible to identify individuals genetically predisposed to disease.

We are now in the early stages of a new era of genetic knowledge and technology that could result in the next quantum leap in our understanding of the nature and function of the human organism and the genetic mechanisms of disease. New DNA technologies make it possible to see the genetic material, to identify the particular sequence of each gene, and to correlate specific genes with their normal function in the human organism. Similar to the discovery of the microscope and x-ray, the new genetic technologies have the potential to revolutionize health care by making it possible to recognize individuals who have or are susceptible to diseases with a genetic component.[60]

There are four approaches to controlling genetic disease: prevention, gene therapy, treatment, and avoidance.

The ultimate objective is to understand the series of events leading from the cause to the clinical manifestations of disease, and then to use the knowledge to prevent or treat the disorder. There are four potential approaches to reducing the burden of genetic disease: disease prevention, gene therapy, treatment of incipient or established disease, and avoidance. Prevention is the ideal, and one way it can be achieved is by reducing the mutation rate. Where this is not possible, the options include prevention of the disease by controlling the associated risk factors, gene therapy to offset or correct the mutation, or treatment to address the consequences of the mutation. Finally, for families at known risk, a number of approaches are available to avoid the birth of affected children.

Canada has been a pioneer in the development of genetic technologies and services.

Accurate prediction of risk and accurate diagnosis of genetic disease are important components of disease control. Genetic diagnosis, screening, counselling, and treatment are the foundations of genetic health services, and Canada has been a pioneer in developing diagnostic, screening, and treatment technologies, and in establishing disease registries.

DNA Technologies for Diagnosis of Genetic Disease

Diagnosis of genetic disease (see Box 11) is based on:

Diagnosis can be made at many levels.

- chromosomal structure and number;
- DNA sequence (using gene probes or markers);
- the amount, character, and function of the gene's protein product;
- any measurable metabolic or biochemical effects that are characteristic of the disorder;
- all associated clinical manifestations.

Diagnoses based on clinical signs have major drawbacks.

Diagnostic technologies based on metabolic products or clinical signs have a major disadvantage: by the time such diagnosis is possible, the disease may be established and irreversible harm done. Moreover, these diagnostic methods do not pinpoint the precise genetic cause of the disorder and are therefore frequently less useful in establishing prevention and treatment programs.

Box 11
Examples of Methods Used in Genetic Testing

Indirect Tests

Maladaptive genes produce metabolic changes that can sometimes be measured to indicate the presence of incipient genetic disease. The substances measured may or may not be involved in causing the disease but are nevertheless associated with its presence.

Example: Phenylketonuria is a single-gene disease that causes mental retardation unless treatment with a special diet begins shortly after birth. The disease results from a genetic defect that prevents the breakdown of phenylalanine. As a consequence phenylalanine builds up in body fluids.

There are mass screening programs in place across Canada to detect disorders of phenylalanine metabolism in newborns. The screening test measures the level of phenylalanine in a blood sample taken from the newborn.

Gene Product Tests

The proteins derived from maladaptive genes can be measured directly to identify some diseases. The test must differentiate the abnormal form or activity of the protein from its usual form or activity.

Example: People with sickle cell anaemia possess an abnormal form of haemoglobin that causes red blood cells to change shape when the oxygen supply in the blood is below a certain point (e.g., during ordinary physical movement). The changed shape causes the cells to clump together, blocking blood vessels and interfering with circulation. The results can be fatal.

The abnormal blood cells produced by the sickle cell gene can be recognized by their abnormal sickle shape.

Chromosomal Analysis

Some genetic diseases involve very large alterations in the genetic material. Reliable techniques for examining chromosomes have been available for more than 30 years. Aberrations in number or structure (e.g., large insertions, deletions, or rearrangements) of chromosomes can be observed.

Example: Down syndrome is usually caused by the presence of an extra copy of chromosome 21. To reach a diagnosis, cells from an individual are treated so the chromosomes can be seen and distinguished from one another when magnified and photographed. This process is called karyotyping.

Recombinant DNA Technology

This technology can be used to establish the presence of, or potential for, disease involving genetic alterations as small as a change in one nucleotide. Recombinant DNA tests rely on the fact that a single strand of DNA will bind to another strand if it contains the complementary sequence of nucleotides.

Genetic Markers

The presence of, or susceptibility to, a genetic disease can be ascertained through use of genetic markers, even when the mutation causing the disease has not itself been identified. Markers are characteristic nucleotide sequences that are associated with, but are not necessarily the cause of, the disease or susceptibility.

Example: Huntington disease is a neurological disorder whose symptoms begin in adulthood and include uncontrollable limb movements and mental deterioration. Diagnosis is now possible in some families before the symptoms of the disease appear. The risk of developing Huntington disease can be assessed by finding out whether a DNA sample from a person at risk for the disease binds to specific DNA strands containing the relevant genetic marker. A person with one parent affected by the disease has a 50 per cent chance of inheriting the disorder; currently available DNA testing may reduce the uncertainty over whether that person has inherited the disorder to 4 per cent.

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Diagnostic technologies based on knowledge of precise DNA sequences have several advantages. Because the DNA is present from the moment of fertilization, tests based on analysis of DNA can identify risk before the onset of any symptoms or damage. In addition, since an individual's full complement of genes is present in the nucleus of every cell, it is always possible to examine DNA, whereas the enzyme or metabolite of interest may not be present in all cells. The gene may be active only in certain tissues and at certain times; the gene products may be located in tissues that are difficult to sample, such as the eye or brain. However, there are still several useful applications for tests based on gene products and metabolites (e.g., the test for Tay-Sachs disease and screening for phenylketonuria).

Diagnostic techniques based on precise DNA sequences have several advantages.

Technology now exists to scan genetic material for the presence of specific mutations. If the DNA sequence of the mutation causing a disease (or a predisposition to a disease) is known, the mutation can be detected using a gene probe. If the precise mutation is not known it can often be inferred using a genetic marker.[61] The first disease-specific marker — for Huntington disease — was identified in 1983. There are now markers for several hundred genetic disorders and the list is growing rapidly (see Box 12). In contrast with methods that identify the mutation itself (direct methods), diagnosis by association with markers (indirect methods) requires family studies.

If the DNA sequence causing a disease is known, it can be detected using a gene probe.

If the precise mutation is not known, it can often be inferred using a marker.

Screening and Diagnosis

Genetic screening is a search in a population to help identify individuals who may have or be susceptible to a specific genetic disease, or be at risk for having children with the disease. Screening programs may be used as a part of diagnosis and health care delivery geared to individual needs. Screening can assist in prevention or treatment of disease, help provide reproductive options for those at risk of having children with serious genetic disease, and be used as a research tool to study genetic variation, or specific mutations and their causes and health implications.[62]

Genetic screening identifies those individuals in the population who may have or be susceptible to a specific genetic disease.

Screening is an initial step; more precise tests are required later for definitive diagnosis. A variety of screening technologies and programs exist, targeted to different disorders, age groups, and stages of disease (including carriers of genetic diseases, fetuses, newborns, pre-symptomatic individuals and individuals with symptoms).[63] There are disorders for which screening programs can be effectively applied on a national level (e.g., phenylketonuria) or on a subset of the population (e.g., the screening of the Ashkenazi Jewish population for Tay-Sachs disease). The types of screening programs and Canadian examples are outlined in Appendix 3.

Screening is an initial step. More precise tests are needed for definitive diagnosis.

Most screening tests at present measure enzyme or metabolic effects rather than changes in the DNA itself. For example, the disease phenylketonuria (PKU) results from an inability to metabolize phenylalanine, one of the essential amino acids. This inability can result from a number of different mutations in the relevant genes. The prognosis and treatment vary according to the specific mutation. Screening of newborn populations based on a chemical test that detects an elevated level of phenylalanine in the blood will identify all those with an elevated level. More detailed testing of the identified individuals will indicate the precise cause and, hence, the most appropriate treatment.[64]

Most current screening tests look for biochemical effects rather than changes in the DNA.

Box 11 (continued)

Gene Probes
These work on the same principle as genetic markers but use strands of DNA that contain the actual sequence of the genetic mutation that causes the disease.

Example: Haemophilia A results from an inability to make factor VIII, a protein involved in blood clotting. Several genetic mutations causing haemophilia A have been identified and diagnosis using gene probes is now possible.

Box 12 Mutant Genes and Genetic Markers

Examples of disorders for which mutant genes have been characterized:
Cystic fibrosis
Duchenne muscular dystrophy
Haemophilia A
Phenylketonuria
Premature coronary artery disease
Retinoblastoma
Sickle cell anaemia
Tay-Sachs disease
ß-Thalassaemia
Von Willebrand disease

Examples of disorders for which genetic markers are available:
Adult-onset polycystic kidney disease
Familial Alzheimer disease (in some families)
Fragile-X mental retardation
Huntington disease
Myotonic dystrophy
Neurofibromatosis
X-linked retinitis pigmentosa

Box 13 Phenylketonuria Newborn Screening: An Example of the Effectiveness of Genetic Health Services

- The major effect of phenylketonuria (PKU) is mental retardation. Twenty-five years ago it accounted for 1 per cent of admissions to institutions for the retarded in Canada.
- About one in 10 000 newborns has PKU.
- A liver enzyme (phenylalanine hydroxylase) is deficient in a person with PKU. This enzyme converts phenylalanine, a substance absorbed from food, into other products. If phenylalanine is not converted, it accumulates in body fluids and causes brain damage. These effects can be prevented by a diet controlling the intake of phenylalanine. Diagnosis in the first month of life and continuous treatment thereafter prevents mental retardation.
- Women with PKU give birth to mentally retarded babies in the vast majority of cases unless they maintain a phenylalanine-controlled diet throughout pregnancy. Elevated phenylalanine levels in the mother interfere with the development of the child she carries.
- There is currently a register of women with PKU in Quebec and a study of the long-term effects of dietary interventions during pregnancy on the children of these women is under way.

Baby G was her parents' first child. She was born before newborn screening programs for PKU were established in Canada. At six months she showed delayed development, and at nine months uncontrollable seizures began. Investigations revealed she had phenylketonuria. Today at age 28 she is very retarded and requires custodial care.

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The ability to screen for and diagnose diseases with a genetic determinant is improving as a result of our growing knowledge of DNA sequences and gene-disease links.

Prevention

Prevention of genetic disease can be achieved in a number of ways.[65] All measures that will reduce the mutation rate constitute primary prevention; they include control of exposure to ionizing radiation and chemical mutagens. Secondary prevention addresses interacting risk factors for genetically predisposed individuals (e.g., controlling diet for those at risk for heart disease). Another form of secondary prevention compensates for the defective gene. For instance, the special diet given to patients with PKU is low in phenylalanine to prevent metabolic imbalance and associated brain damage (see Box 13).

Genetic diseases can be prevented by reducing the mutation rate, controlling the risk factors, or compensating for the defective gene.

Our present understanding of the cause of mutations and of interactions between genetic predisposition and environmental risk factors in multifactorial disease is not yet sufficient to prevent most diseases. But the knowledge we do have already has some useful applications. For example, new knowledge about a risk factor (familial hypercholesterolaemia) for heart disease shows that a serious predisposition can be treated to reduce the occurrence of heart disease or improve the prognosis once the disease is present.[66]

However, our current knowledge is not sufficient to prevent most multifactorial diseases.

Gene Therapy

Gene therapy for genetic disease is the attempt to correct the intrinsic defect in the genetic material. Correction of a genetic defect is a complex process.[67] The DNA sequence of the functional gene must be known and the genetic material available. A vector or agent is needed to deliver an effective dose of the therapeutic sequence to repair the natural condition, while doing no harm. The therapeutic DNA sequence must be introduced at the correct location in the overall DNA sequence, without causing damage to the DNA. The therapy must result in the desired effect in the right tissues at the right time.

Gene therapy involves correcting the defect in the genetic material.

There are two forms of gene therapy; one involves inserting the DNA sequence into germ line cells, whereas the other uses non-germ line (or somatic) cells. Changes to germ line cells can be passed along to subsequent generations. Changes to somatic cells affect the individual receiving the therapy, but the changes are not transmitted to offspring.

No proven gene therapies are available to cure genetic disease at this time. Intensive research will undoubtedly yield somatic cell gene treatments for some disorders. Potential applications include, for example, treatment of sickle cell anaemia and thalassaemia by reintroducing treated cells into bone marrow. Repair of germ line cells is unlikely in the foreseeable future, and for many diseases gene therapy may never be a viable option.

No proven gene therapies are available yet.

In September 1990 a four-year-old American girl became the first person to undergo somatic cell gene therapy in an attempt to treat a genetic disorder (severe combined immune deficiency disease). Research involving such treatment is under consideration for a number of other disorders.[68]

Box 13 (continued)

Her sister, R, was born three years after G. On the third day of her life, genetic testing showed that R also had phenylketonuria and treatment was started on the same day. Today, R is a university graduate and leads a normal, healthy life.

Canada has been in the vanguard for universal newborn screening, early diagnosis, and treatment of PKU. Through a national food bank for genetic patients, treatment is available for this disease and many others like it. Mental retardation due to PKU has virtually disappeared in Canada since the inception of newborn screening and access to treatment.

Box 14 Tay-Sachs Disease: Prenatal Diagnosis and the Choice for Healthy Children

- Tay-Sachs disease is a degenerative disorder that affects the neurological system, leading to blindness, mental retardation, and death in early childhood.
- In the general population the disease is rare, occurring once in approximately 400 000 births. But it is much more frequent in specific populations. Approximately one in 30 individuals of Ashkenazi Jewish descent carries one copy of the gene that causes the disease when present in a double dose. One in 3600 infants from this group has the disease. Tay-Sachs disease has also turned up with higher than average frequency in the French Canadian population.
- Studies of the Tay-Sachs gene have shown there are several different mutations causing the disease. Two different mutations occur in the Canadian Jewish population. Another mutation that has not been identified in Jews occurs in French Canadian families with a history of Tay-Sachs disease; and there are yet other mutations in French Canadians.

Mr and Mrs S's first child was a healthy boy. Their second born (B) was also a boy. At six months, B could not sit and his head was enlarging. He died in early childhood of Tay-Sachs disease: paralyzed, mute, blind, wasted, with a head too large for his body. There is no treatment for Tay-Sachs disease.

When the enzyme deficiency in Tay-Sachs disease was discovered in 1969, it became possible to identify carriers of the Tay-Sachs gene. Two large screening programs were established in Canada in the early seventies. Follow-up studies show that screened persons have positive views about the procedure. Carrier couples have used prenatal diagnosis to deal with the risk of having an affected child.

After Mr and Mrs S lost B they wanted to have another healthy child. Two pregnancies were monitored and both the fetuses had Tay-Sachs disease; the parents had the option to terminate and they did. They tried once again. Mrs S carried an unaffected fetus to term and delivered a healthy girl. She is now 12 years old. Meanwhile, the incidence of Tay-Sachs disease in Canada has fallen strikingly in the past two decades.

Gene therapy entails a risk to the individual receiving the therapy and a potential long-term risk to the species. All attempts to treat disease through gene transfer should be subject to guidelines equivalent to the Medical Research Council guidelines for both research involving human subjects and gene therapy research.[69] All proposed research and treatment technologies will have to be carefully evaluated.

Gene therapy poses a potential risk to individuals.

Treatment

When prevention is not possible, the identification of individuals at genetic risk or at the stage of incipient, instead of established, disease can lead to a better prognosis through earlier diagnosis and treatment, as in the case of some familial cancers. Understanding the cause of disease helps to tailor the treatment to the specific problem; this is true for pneumonia and equally true for heart disease, leukaemia, hypertension, and numerous other disorders. At present, there are relatively few effective treatments. This scarcity partly reflects the lack of knowledge about the cause and course of most genetic diseases.[70]

Earlier identification of susceptible individuals may improve treatment and prognosis.

Avoidance

The term avoidance is used to cover technologies and strategies to avoid the birth of children with serious genetic disorders. Avoidance strategies include deciding not to have a family, prenatal diagnosis (with the option of terminating the pregnancy if the fetus is affected), and alternative methods of having children, such as adoption, artificial insemination, or other reproductive technologies.[71]

Technologies and strategies are available to help avoid the birth of children with serious genetic disorders.

At this time, families faced with a high risk of serious genetic disorder in their offspring often regard prenatal diagnosis as the best option available to them for having healthy children (see Box 14). Technologies for prenatal diagnosis, although not available for all genetic disorders, are more advanced than technologies for prevention or treatment. However, some women choose not to undergo prenatal diagnostic testing. One reason is that the procedure may damage a normal fetus. Currently, the additional risk of losing the fetus is about one in 200 during amniocentesis and a little higher during chorionic villi sampling procedures.[72] Some who refuse the test do not want to be faced with a decision about terminating their pregnancy. Others simply do not consider it an option because of their views on pregnancy termination.

Prospective parents who are at risk often consider prenatal diagnosis their best option.

Prenatal testing may be refused for fear of damaging the fetus.

Factors affecting the willingness of women to undergo prenatal diagnosis include the degree of risk that the diagnostic procedure will harm the fetus, the accuracy of the diagnostic test, the probability that the fetus has the disorder, and the severity of the disorder and its health implications.[73]

The attitudes toward prenatal diagnosis highlight the need to develop diagnostic procedures that are less invasive and thus pose less risk to the fetus. Also required are methods that provide genetic information earlier in the pregnancy, perhaps even before fertilization. The ultimate objective is to remove the need for prenatal diagnosis by finding cures for genetic diseases.

There is a need for prenatal diagnostic procedures that give earlier results with less risk to the fetus.

Box 15
Thalassaemia: An Example of the Need for Continuing Research into Genetic Disease

- Thalassaemia is the most common identifiably genetic disease in the world. Approximately 3 per cent of the human population carries a thalassaemia gene.
- People inheriting one thalassaemia gene (carriers) have a harmless mild anaemia (thalassaemia minor). People inheriting two thalassaemia genes have a fatal anaemia (thalassaemia major).
- Current treatment for people with thalassaemia major includes blood transfusions and treatment to remove the resulting excess build-up of iron in the body's tissues. These measures prolong life into the third decade. In the future, gene therapy involving insertion of normal genes into bone marrow may prolong life further and reduce the need for treatments, which are painful.
- Thalassaemia genes have been perpetuated in human populations because they confer a selective advantage: they protect carriers from malaria.

At 27 years, H is the oldest person with thalassaemia in Quebec. His parents came to Canada from a malarial region of Europe. H recently married. He and his wife advocate the simple test that identifies persons carrying a thalassaemia gene. Carrier couples receive genetic counselling, and have the option of prenatal diagnosis to avoid having a child with the disease (a 25 per cent risk). The Quebec thalassaemia screening program now screens 80 per cent of high school students in the communities at high risk. The Quebec program is the largest on the continent and among the most effective in the world at avoiding thalassaemia disease. Meantime, H is waiting for advances in treatment or gene therapy.

Use of avoidance-related technologies requires careful consideration of the ethical implications. A caring society will also ensure that the availability of prenatal diagnostic technology does not diminish efforts to develop better disease treatments and therapies (see Box 15).

Counselling

The purpose of genetic counselling is to provide the medical and genetic facts, to describe the risk of recurrence of disease and the options to avoid recurrence, and to assist the individual or family in coping with this information.[74] The Canadian approach to counselling recognizes the autonomy of the client and the primary responsibility of the counsellor to the client, rather than to the species or future generations.[75]

Counselling provides information and support; the primary responsibility of the counsellor is to the patient.

The Canadian College of Medical Geneticists has a good general policy relating to counselling,[76] but more comprehensive guidelines dealing with specific topics, such as confidentiality and full disclosure, are needed. The report of the U.S. President's Commission, *Screening and Counseling for Genetic Conditions* (1983), provides an excellent outline of specific topics from which additional guidelines particular to the Canadian context could be developed as required.[77]

Additional guidelines are needed to deal with some difficult counselling issues.

Current Technology Limitations

The use of DNA-based diagnostic technology is growing but has, and probably always will have, limitations because of the complexity of the human genome and the consequences of natural genetic variation. Whereas some mutations (e.g., sickle cell anaemia) are common and the related test can be applied across a large population, most mutations are less common, even rare. In cases where the mutation is not yet known, the patient must be studied in the context of his or her family. For this, other family members must be available and willing to cooperate.

The use of genetic diagnostic technology does have its limitations.

In many cases, genetic testing is based on linked genetic markers. But the presence of the marker does not mean that the disease-causing mutation is present. The frequency with which the marker and the disease-causing mutation are found together depends on the proximity of the marker to the gene.

Even evidence that the mutation is present does not necessarily mean that the individual will develop the illness. Moreover, while some genetic diseases have a predictable outcome, others vary in their severity, age at onset, and prognosis. For example, expressions of the gene for neurofibromatosis vary from a few coffee-coloured skin spots to major tumours and seriously handicapping systemic involvement. These differences may arise from the effects of other genes or from environmental factors that either amplify or suppress the effect of the neurofibromatosis mutation. Differences may also reflect the fact that a number of different mutations are "lumped together" as a single condition.

Even if a specific mutation is present, it is not always possible to predict whether the individual will develop the related illness or how serious the disease will be.

Even in disorders where the specific mutation and subsequent effects are well known, it does not necessarily follow that an effective treatment is available. At present, the ability to identify an individual at risk for genetic diseases exceeds the ability to prevent or effectively treat the disease. This limitation is likely to continue for some time and implies that knowledge of

Our ability to identify susceptible individuals may continue to exceed our capacity to prevent or treat their diseases.

presymptomatic genetic disease or risk of disease is not necessarily beneficial. Although the genetic technologies hold great promise, we do not know yet how successful researchers will be in developing technologies to prevent or treat most genetic diseases. In 50 years we may have significantly more cures and treatments. Or we may primarily have more and better diagnostic and predictive capability.

Some disorders will remain difficult or impossible to treat for the foreseeable future.

The genetic diseases receiving the greatest attention from researchers are the classic, single-gene, inherited disorders and common disorders. The classic, single-gene disorders are of interest because diagnostic and treatment technologies should be easier to develop, at least in theory. Common disorders are of interest because their technologies have the potential for wide application. Genetic tests and therapeutics for the majority of genetic diseases, which are neither classic nor common, may be a long time coming.

Uncertainty

Genetic tests are most useful when they translate uncertainty into certainty.

The risk of occurrence of disease is often expressed in terms of probability. Such risk statements cause difficulties in several ways. Tests that simply indicate a probability of the disorder being present, or a degree of risk, are of less help to the person who must decide on a course of action than tests that confirm the presence or absence of the disorder. Uncertainty is generally undesirable; certainty — even of having a disease — has its advantages if courses of action are available. As well as pertaining to whether an individual has a disorder, certainty can refer to the conditions under which a susceptible individual will develop the disorder, or to the disease outcome. The better the information, the more informed the choice the individual can make.

Risk statistics may be difficult for a patient or family to understand.

But understanding a risk, and then going one step beyond that to accept or reject the risk, is difficult for most people. Numerous factors influence how an individual interprets risk of disease.[78] Our understanding of risk statistics and our attitudes toward the disease are major variables.

An individual's perception of risk is affected by the manner in which risk information is presented.

The manner in which probability is presented also affects an individual's perception of risk. The following two statements, which describe the same degree of risk, can be viewed quite differently by prospective parents: "There is one chance in four that your child will be born with a genetic disease," versus "There are three chances out of four that your child will not have this disease."

The development of better predictive technologies will help reduce the uncertainty. We need technologies that turn uncertainty into clear statements about the presence or absence of the disorder, or the predisposition to the disorder. However, some uncertainty will still remain over whether individuals susceptible to a particular disease will actually get the disease. There is also a need to help individuals to understand the meaning of risk and to assess the trade-offs associated with uncertainty.

Prerequisites for Use of Technologies

The objective of genetic health care should be to deliver reliable and cost-efficient services.

All technologies delivered in Canadian health care systems should provide reliable and cost-efficient services. Decisions about provision of a specific health technology are influenced by the prevalence of the related disease in the

population, the severity of the disorder, social attitudes, ethical considerations, treatment options, the availability of other technologies, and costs.

To be useful, genetic technologies must first indicate reliably whether the mutation is present or absent. The technology must offer the individual real benefit in terms of disease prevention, treatment, avoidance, or planning. The number of useful applications of genetic technologies is growing.

Services should offer a real benefit in terms of disease prevention, treatment, avoidance, or planning...

A major component of a compassionate health care system is its care and support for individuals who are either sick or at risk of developing a disease. Efficacious genetic technologies and services are, and should continue to be, evaluated and delivered in the context of a caring society.

...and should always be delivered in the context of a caring society.

Technology Assessment and Economic Implications

In conjunction with the development of genetic technologies, there is a need for effective review protocols. Any introduction of new genetic tests and treatments for clinical purposes should involve a technology assessment that takes into consideration benefits, safety, ethical implications, and economic consequences, as well as technical matters. Primary requirements for any technology are efficacy and reliability. For genetic tests sensitivity, specificity, and predictive value should be carefully assessed (see Box 16).

Proposed genetic services should be assessed with consideration to safety, efficacy, ethical and economic implications, as well as technical considerations.

The cost implications of new technologies and services have to be considered carefully. Effective cost assessments provide a framework for making decisions on allocation of health care funds. Key elements in economic evaluations include:[79]

- well-defined questions that can be answered by the assessment;
- selection of an appropriate form of evaluation;
- consideration of a comprehensive range of alternative technologies or services;
- evidence of the effectiveness of the technologies or services being compared;
- identification of the range of costs and benefits of each alternative;
- measurement of the costs and benefits in appropriate units;
- adjustment of costs and benefits to reflect their monetary value at the time they are realized;
- an allowance for uncertainty in costs and benefits and estimation of the degree of uncertainty.

There are a number of key elements that must be addressed in economic analysis.

Long-Term Implications

Will genetic technologies have a significant effect on the characteristics and health of future generations? There is no easy answer. The technologies have potential long-term implications through prevention and treatment of genetic disease, and through identification and control of mutation-causing agents.

Consideration should be given to the long-term implications of genetic technologies.

As a species we have for thousands of years encountered — and sometimes introduced — new selective forces in the evolutionary equation. All medical care alters natural selection by assisting individuals in overcoming the effects of disease and leading normal and healthy lives, be it with hearing aids, insulin, or

Box 16
Sensitivity, Specificity, and Predictive Value of Screening Tests

Test Result	Disease Categories of an Apparently Well Population	
	Target Condition Present	Target Condition Absent
Positive	A True Positives: Individuals with the condition and with positive test results	B False Positives: Individuals without the condition but with positive test results
Negative	C False Negatives: Individuals with the condition but with negative test results	D True Negatives: Individuals without the condition and with negative test results

An ideal test would detect only individuals with the condition and would identify all such individuals. Measures of a test's validity include:

Sensitivity = [A/(A+C)] = the probability that the test will correctly identify individuals with the condition.

Specificity = [D/(B+D)] = the probability that the test will correctly identify individuals without the condition.

Positive Predictive Value = [A/(A+B)] = the probability that a person with a positive test will manifest the condition.

Negative Predictive Value = [D/(C+D)] = the probability that a person with a negative test will not manifest the condition.

The closer that each of these measures is to 1.0, the more useful the test.

kidney transplants. Improvements in health care are increasingly postponing death and in that sense are resulting in preservation and transmission of "maladaptive" traits.

Genetic techniques that interrupt the transmission of dominantly inherited diseases will abruptly reduce their incidence. But effective treatment of diseases that would otherwise result in death prior to reproductive age will increase the frequency of the gene in the population. The situation is more complex for recessively inherited disorders. The incidence of such diseases may decrease rapidly through counselling, prenatal diagnosis, or curative treatment, but the number of individuals who are carriers could increase.[80] However, it would take many generations for the number of carrier-carrier matings to rise significantly, allowing time to work toward treatment or prevention of the disorder.

The technologies may reduce the incidence of both dominantly and recessively inherited diseases but increase the number of carriers.

The implications to health in the carrier of "silent" genes vary with the gene, and are still largely unknown. Carriers can have a health advantage. Carriers for blood diseases such as thalassaemia and sickle cell anaemia are resistant to falciparum malaria; this advantage has helped maintain these mutations in human populations. In other cases carriers may be at a health disadvantage. For example, carriers for ataxia telangiectasia appear at increased risk for breast cancer.[81]

The health implications of carrier status vary from gene to gene.

Identification of mutagenic agents in the environment may lead to long-term improvements in human health. Regulations for the control and use of potential mutagens will help maintain an environment compatible with present and future health, and are in the interests of the human race.

Identification and control of potential mutagens may lead to long-term improvements in human health.

Another broad area with potential long-term implications is the development and use of genetically engineered material. Genetic engineering technologies have applications in diagnosis and treatment of disease, but there are serious potential hazards associated with genetically engineered material. In recognition of these hazards, some national and international guidelines and regulatory controls for responsible research, use, and handling of such materials have been put in place (see Box 17). Upgrading of guidelines and controls as appropriate to ensure safe practices must continue.

Development and use of genetically engineered materials also have potential long-term implications.

Guidelines for Screening and Testing

There is a need for guidelines to ensure that genetic screening programs and testing are appropriate and effective. Conditions that should be met by genetic screening programs include:

- that the objectives be clearly defined (whether for effective medical intervention, for family planning, for research, etc.);
- that screening be part of an integrated program that includes counselling, diagnosis, medical management, follow-up, outcome evaluation, and so on;
- that the genetic tests be sensitive, reliable, precise, and predictive;
- that the decision to be tested be based on individual consent (or parental consent in the case of minors), and that all services be available on a voluntary basis, with the exception of some screening programs for minors. In the case of certain serious, treatable disorders for which screening and treatment pose no significant risk, the state may intervene and waive the need for parental consent to ensure that universal screening and access to

Genetic screening programs should meet certain conditions.

Box 17
Guidelines and Regulatory Controls for Genetically Engineered Materials

- Research involving recombinant DNA technology and materials is covered by laboratory biosafety guidelines developed jointly by Health and Welfare Canada and the Medical Research Council. The guidelines recognize that it is impossible to predict all the potential engineered organisms or products used or produced in the course of research. Potential risks associated with recombinant DNA research should be assessed on a case-by-case basis by the biohazards committee at the laboratory proposing to undertake the research. Containment levels appropriate to the level of hazard should be adopted.

- The Medical Research Council guidelines on gene therapy research address long-term implications.

- Therapeutic and diagnostic products have potential long-term implications both because of their intended use and because of the possibility that engineered materials might be released into the environment during the manufacturing process. The licensing of pharmaceuticals, including those involving recombinant DNA in the process or final product, is controlled under the Canada Food and Drugs Act. Licensing takes into consideration safety and efficacy of the product, but does not deal with the issue of environmental release during commercial production.

- The development of commercial products to diagnose genetic disorders may involve use of recombinant DNA materials. Under the Medical Devices Regulations (Canada Food and Drugs Act), the Bureau of Medical Devices must be notified regarding the sale of such products. No information is required regarding safety, efficacy, or environmental implications.

- The environmental release of genetically engineered material is covered in biotechnology regulations currently (1991) being formulated under the Canadian Environmental Protection Act. The regulations will apply to new products, including genetically modified organisms, intended for deliberate environmental release or large-scale production. Release of engineered organisms could also be controlled through development of industry-specific provincial pollution control regulations and guidelines; no such regulations or guidelines are currently in place.

- Many research and commercial applications of recombinant DNA fit readily into existing regulatory mechanisms. Some regulatory modifications are under way to address new issues. However, new products and applications will continue to arise. Biotechnology-related products, processes, and issues that do not readily fit into the existing assessment and control mechanisms are dealt with through the Interdepartmental Committee on Biotechnology, which addresses safety and control requirements for new issues.

early, effective treatment are available. In such cases there is a duty to inform parents;

- that the results and effects of all screening programs be reviewed and evaluated, and that programs be modified as appropriate;
- because screening programs for specific ethnic groups could be used, or perceived to be used, in a repressive or stigmatizing manner, public education should emphasize that everyone is at least a carrier of genes with the potential to adversely influence health status, and that each population has its own particular genetic risks;
- that guidelines for screening programs be adopted by consensus, disseminated, and updated when necessary.

The Canadian College of Medical Geneticists (CCMG) has adopted professional and ethical guidelines for the delivery of genetic services.[82] In conjunction with the Society of Obstetricians and Gynaecologists of Canada, the CCMG has also developed recommendations related to the delivery of prenatal diagnosis of genetic disorders. Comprehensive guidelines will be required to deal with specific issues. For instance, in the case of prenatal diagnosis, a report of the Royal College of Physicians of London could serve as a model for the development of Canadian guidelines. (The report's recommendations are provided in Appendix 4.)

The CCMG has adopted professional and ethical guidelines for delivery of genetic services.

4. GENETIC HEALTH CARE SERVICES IN CANADA

The feasibility of applying genetic knowledge to medical practice, and the health care benefits that can accrue, have been demonstrated in genetic clinics across Canada for decades. The potential for benefits is greater still now that it is increasingly possible, using new DNA technologies, to analyse the genetic determinants and understand better the biological bases of disease.

Genetic technologies offer great potential health care benefits.

There are two interrelated approaches to delivery of genetic services. One approach involves integration of genetic knowledge and technologies into routine aspects of medicine. The other approach involves delivery of specialized services, usually through genetic centres.

There are two interrelated approaches to delivery of genetic services.

Some of the existing Canadian genetic services are widely respected and serve as models internationally. Examples include the maternal phenylketonuria registry and the Network of Genetic Medicine in Quebec, the British Columbia Health Surveillance Registry, and services for Huntington disease, muscular dystrophy, and cystic fibrosis patients and families.[63] Yet, despite these and other successful programs, major problems hamper the delivery of genetic health services in Canada.

Major problems hamper the delivery of genetic health services.

Genetic health services are not well integrated into Canadian health care; they remain largely isolated and treated as an esoteric medical specialty. Even the genetic centres themselves are constrained in their ability to deliver adequate services. These problems indicate that, in general, health care professionals, administrators, and decision makers do not place a high priority on the role that genes play in health, or on the contribution that genetic technologies can make in all areas of health care. Increasing cost constraints, related to rising health care costs, compound the problem.

Integration of Genetic Knowledge into Health Care

Effective genetic services will require better integration of genetic knowledge and technologies into all aspects of health care. To date, physicians and other health care practitioners have not widely incorporated genetic knowledge and tools into their practices. The potential role of genetics in health care extends far beyond the services offered at specialized genetic centres. Genetics has implications for all aspects of health care, from understanding why a specific patient has a particular disease to managing each individual's health and diseases.[64] Eventually, genetic knowledge and technologies will be among the fundamental components of health maintenance and disease control. All health care practitioners will become, to some degree, geneticists.[65]

Health care practitioners have not widely incorporated genetic knowledge and tools into their practices.

Eventually, all health care providers will become geneticists to some degree.

As the role of genetics in health and disease is integrated into medical education and related technical training, it will be possible and appropriate to decentralize testing, diagnosis, and treatment and to integrate genetics into all health care specialties, including family practice.

Genetic Centres

At present, most genetic diagnostic testing, treatment, and counselling is carried out in a few major genetic centres across Canada. Eight centres for training and service delivery are currently accredited by the Canadian College of Medical Geneticists. There are twice as many centres offering some specific genetic

More than 25 centres offer some genetic health services. Services include diagnosis, counselling, and treatment.

health services. In addition, the provinces and territories incorporate some services, including screening programs for newborns and population-specific carrier screening programs, into their general medical administration (see Appendix 3). Genetic services and patient follow-up are also sometimes handled through clinics oriented to a particular disease.

The centres offer services oriented to individuals, families, and populations.

The genetic centres offer services oriented to individuals or families, and to certain populations. Referrals to genetic centres are made for a number of reasons including occurrence in the family of disease thought to be genetic, frequent miscarriages, or abnormal fetal ultrasound results.

The referred "patients" are often families rather than individuals. Each case involves an average of 2.7 family members.[66] A Science Council survey of 10 genetic centres found that over a one-year period (1986-87) the centres dealt with almost 19 000 cases, thus treating and counselling more than 50 000 individuals.[67] Most of this activity focused on diagnosis; counselling on prognosis, risk of recurrence, and reproductive options; and treatment to alleviate symptoms and prevent complications (often long-term treatment involving support for the patient's family). Approximately 50 per cent of referrals involved prenatal diagnosis.

In 1986-87, about half of all referrals were for prenatal diagnosis...

...and only 5 per cent of lab tests were based on the new molecular DNA technologies.

In the survey period, the centres conducted more than 40 000 laboratory tests. Sixty per cent of the tests were biochemical, 35 per cent were cytogenetic, and 5 per cent were molecular. The number of molecular tests is low because the technologies are new. Only four centres analysed molecular samples, although several centres counselled patients based on results of molecular testing. Analysis of samples from population screening programs is usually done by central provincial laboratories, but genetic centres generally undertake counselling and follow-up.

The Science Council survey indicated that:

The full range of genetic technologies is not uniformly accessible to all Canadians and waiting lists for services are long.

- genetic health care technologies and services are not uniformly accessible to all Canadians;
- 80 per cent of the centres were unable to meet the current demand for laboratory and clinical services;
- waiting periods ranged from one to 10 months. Priority is given to families requiring prenatal diagnosis because the information is needed promptly;
- the administrators of Canada's health care systems have not adequately prepared for the current availability of, and the anticipated increase in, genetic technologies and the subsequent demand for services;

Genetic programs are continually struggling for funding.

- Canadian genetic programs are continually struggling for funding. Several programs are funded not through the health care system, but through research and education budgets;
- resource constraints and the priority given to prenatal diagnosis are limiting the availability of other genetic services, including treatment procedures that keep persons with genetic risk factors healthy and productive.

Over the next five years, referrals for existing services are expected to increase significantly.

Respondents at the centres estimated that over the next five years referrals for existing clinical genetic services would increase by 40 per cent, with demand for associated laboratory services increasing by 65 per cent. The demand for molecular genetic tests is anticipated to undergo the greatest growth — an increase of 160 per cent.

The centres were unable to estimate the future demand resulting from the increasing number of genetic tests that are becoming available, or the effect of the growing awareness of genetic services among the public and physicians. Among the new genetic programs that could become available over the next five years is carrier and prenatal screening for cystic fibrosis. The centres considered it unlikely that testing for multifactorial disorders would become widely available within the next five years.

Nevertheless, future demand for genetic services is likely to be substantial. In the United States it has been estimated[48] that once services become available, each year:

- 2.7 million genetic tests will be conducted to detect young women who are carriers of cystic fibrosis, sickle cell anaemia, haemophilia, or Duchenne muscular dystrophy. It is anticipated that testing will identify 49 900 carriers. The additional testing of male partners of these carriers will identify an estimated 2000 male carriers.
- 2.4 million tests will be conducted to detect chromosome abnormalities in pregnant women/fetuses.
- when DNA-based tests become available for screening common diseases such as insulin-dependent diabetes, coronary heart disease, lung cancer, breast cancer, bipolar affective disorder, and Alzheimer disease, 16.2 million tests will be conducted to identify individuals at risk; 810 000 of these tests will be positive.

New tests will result in increased demand for genetic services.

The 10 genetic centres surveyed identified several constraints that hamper their ability to deliver services effectively. Chief among these constraints is a lack of resources, trained personnel, and awareness on the part of health care providers and planners.

Lack of Funds

It is difficult to estimate the resources allocated to genetic centres because the mechanisms and sources of funding vary. A total annual operating budget of $10 million was estimated for the 10 centres surveyed by the Science Council.

Few genetic centres are funded entirely by the health care system; their funding derives from a mixture of research and education as well as health care dollars. The centres experience particular difficulty in obtaining funds to deliver verified new technologies. In addition, little funding is available for purchase of capital equipment or evaluation of new and proposed services. Capital purchases are generally funded through hospital budgets, although provinces sometimes fund the start-up costs of new or expanded programs separately.

The centres experience particular difficulty in obtaining funds to deliver verified new technologies.

Salaries of non-physician staff members at genetic centres are usually paid through operating budgets. Physicians providing services in the centres surveyed were paid from a variety of sources including provincial medical insurance programs (fee-for-service), universities, provincial genetics programs, and hospitals. Many of the geneticists surveyed felt that fee-for-service payment was unsuitable to the nature of the work and not conducive to the integration of genetic practices into other health care specialties. This form of financing does not accommodate the amount of time required to develop genetic histories, to perform and interpret tests, and to provide counselling

Fee-for-service funding hampers integration of genetics into health care.

Box 18
Available and Needed Personnel for Delivery of Genetic Health Services

The 1985 manpower survey conducted by the Canadian College of Medical Geneticists (CCMG) recognized an immediate shortfall of 34 full-time-equivalent (FTE) positions. Canadian health care personnel delivering genetic services consisted of:

- 43 FTE medical geneticists;
- 40 FTE "other professional staff."

The CCMG estimated the personnel required to provide adequate genetic services at:

- 65 FTE medical geneticists;
- 52 FTE other professionals.

The survey also predicted that an additional 43 FTE positions would be necessary by 1991. The need for trained medical geneticists and other genetics professionals will continue to grow rapidly as genetics-related technology and health care applications increase.

services for the patient and the patient's family. The average time required for a genetic consultation is three hours spread over two or more sessions.

Lack of Trained Personnel

Another limitation to service delivery is the lack of individuals trained in applied human and medical genetics. At present, the number of medical geneticists and genetics associates in Canada falls considerably below a World Health Organization recommendation[89] that one person with professional training in medical genetics be available for every 200 000 people in the population (see Box 18). The guideline itself was established before most of the new technologies, such as prenatal diagnosis, became available, and is now considered an underestimate.

Service delivery is also limited by a lack of medical geneticists and genetics associates.

There is a particular need for genetics associates. Associates are graduates of a master's-level professional program that is accredited by the Canadian College of Medical Geneticists. Working as part of a genetics team, they assist in the specialized, labour-intensive work involved in diagnosis and counselling. Although the number of available genetics associates is growing, it is not growing quickly enough because there is only one training program in Canada (at McGill University).

The delivery of genetic services and the training of personnel are complicated by the large and increasing number of identified genetic disorders and syndromes. There is a need for more computer-based information systems such as POSSUM (Pictures of Standard Syndromes and Undiagnosed Malformations),[90] both to help in the education of health care practitioners and to provide ongoing assistance in the diagnosis of genetic diseases. Such systems correlate a keyed-in description of symptoms with the disorders or mutations that could be their cause.

There is also a need for more computer-based information systems to assist in training and diagnosis.

Referral

Referral rates at genetic centres are far lower than the known incidence and risk of genetic disease would lead us to expect, and many clients are self-referred. In general, links between medical genetics and other health care disciplines at professional and administrative levels are not well established. For example, young patients with ischaemic heart disease are often not referred for genetic evaluation — a missed opportunity for preventing heart attacks in the next generation. The limited use of prenatal testing for Down syndrome also illustrates the point. The test is sensitive and can detect more than 99 per cent of cases. However, no more than 60 per cent of high-risk mothers (those 35 years of age and over) receive the test, and delivery of the service varies greatly from province to province. In a significant number of cases, the test is not offered to high-risk mothers. The reason that some doctors do not mention the procedure to their clients may be related to lack of knowledge, concern over the risks of the amniocentesis procedure, or their personal feelings on prenatal diagnosis and pregnancy termination.[91] Physicians should be aware of the role of genetics in health care, and of their responsibility to advise their patients of the existence and availability of genetic services.

Referral rates are lower than expected and many clients are self-referred.

Box 19
Health Expenditures in Canada

The value Canadians attach to their health care system is reflected in the magnitude of the resources it consumes.

- In 1987, public and private expenditures on health care in Canada totalled $47.9 billion or $1869 for every Canadian. This amount constituted about 9.0 per cent of the gross national product (GNP). Although absolute expenditures on health care have increased at a rate exceeding inflation, the proportion of GNP spent on health care has remained relatively stable since 1982.
- Canada falls just above the average among OECD countries in terms of resources spent on health care as a percentage of the gross domestic product (GDP). For example, in 1984 the United States spent approximately 10.7 per cent of its GDP on health care. The corresponding amounts for Canada and the United Kingdom were 8.4 and 5.9 per cent, respectively.
- Since 1975 approximately 75 per cent of total health expenditures in Canada every year have been publicly financed.
- Provincial governments currently spend 25-35 per cent of their budgets on health care.

Institutional health care dominates resource allocation.

- In 1987, the operating expenditures of hospitals accounted for about 40 per cent of total health expenditures and other institutions consumed another 12 per cent. Hospitals receive 90-95 per cent of their funding from government sources.
- Professional services consumed 23 per cent of national health expenditures. More than two-thirds of payments for professional services went to physicians.
- The remaining health expenditures were split between a large number of categories, including drugs and appliances (14 per cent) and public health services (4 per cent).
- Less than 1 per cent of total health resources were expended on research. This percentage has remained almost constant since 1970.

Box 20
Genetic Disease and Health Care Services: Opinions of Non-Governmental Organizations

Major findings from the Canadians for Health Research survey of 47 non-governmental organizations:

- There was wide recognition of the role of genetics in the disorder the groups represent or deal with.
- Current genetics-related programs and services were perceived as inadequate or inconsistent.
- The groups identified a need for more genetics-related health services, screening programs, counselling, and family support.
- More than 50 per cent of the organizations identified the need to address ethical issues associated with genetic research or services.
- A need for more research, including targeted research, and research funding was identified.
- There was wide agreement that better education of the public and health care providers on genetics in health and health care is needed.
- Many organizations believe they can play a greater role in advancing the "genetic point of view" in health care.

Planning

The need for effective planning for genetic services is critical as a consequence of rising demand for a growing number of services, and increasing competition for health care resources. The shortfall between supply and demand of services is increasing in all provinces.

The need for effective planning is growing.

Five provinces — British Columbia, Alberta, Ontario, Quebec, and Newfoundland — have established provincial advisory committees on genetic services. The committees vary in format and responsibilities, but essentially they review proposed technologies, the need for genetic services, and the services and budgets of provincial genetic centres. The committees assist in the efficient and rational allocation of services and funds, and they have had some success in developing genetics programs and ensuring efficient, coordinated services. There is a need for such committees in all provinces and territories.

Five provinces have established provincial advisory committees on genetic services.

The future delivery and growth of effective genetic services will depend, in part, on the development of new technologies. But the ability of the advisory committees and other interested groups to make an effective case for services and resources will also play a crucial role. Allocations will be strongly influenced by the economic climate, how the ethical issues associated with genetic technologies are handled, and the degree of awareness among the public, the health care community, non-governmental organizations, and other advocacy groups.

Future delivery and growth of services will rely on the development of new technologies and stakeholder support.

Economic Considerations

Canadians value their publicly funded health care systems but express growing concerns over the quality and accessibility of health care. At the same time, governments are concerned over costs. The rising cost of health care has resulted in a strong push for cost containment, and is making it increasingly difficult to obtain funds for new or preventive technologies. This is the health care environment into which the developing genetic technologies are being introduced (see Box 19).

Public health care systems must balance quality, accessibility, and cost.

Partly as a result of these cost restraints, the principle of accessibility to publicly funded health care is not being upheld for individuals with genetic disease. And yet some services for the prevention of genetic disease use fewer resources than the alternative treatment services.[92] For example, the provincial programs for newborn screening for hypothyroidism and the related treatment to prevent retardation are less expensive than the long-term care of individuals whose disease is diagnosed late.[93] However, at present there is no evidence that, overall, preventive genetic technologies will reduce the costs of health care. All that can be said for now is that genetic technologies have the potential to contribute to better health of Canadians (through better disease prevention and treatment) and to more cost-effective use of health care resources.

Genetic technologies have the potential to contribute to better health of Canadians and to more cost-effective use of health care resources.

The current and developing genetic technologies represent an investment in the health of Canadians that should be considered by those who make funding decisions. Failure to integrate technologies and services within publicly funded health care systems may foster the development of a two-tier system based on ability or inability to pay for privately offered services.[94]

The problems encountered in obtaining funding for genetic health services focus attention on the need for decisions on the role and funding of Canadian health care systems. Public participation in this process is essential.

Role of the Private Sector

At present, the private sector does not play an important role in the delivery of genetic services.

At present, the private sector does not play a significant role in the delivery of genetic services. Private sector labs could offer genetic analysis in the same fashion as radiology services are currently offered, with the physician acting as contact point for referrals and results.

Private sector participation is desirable if the services are publicly funded and meet appropriate standards.

Private sector participation in the delivery of genetic health services is desirable, but there are two specific concerns. If the services are not publicly funded and are available only by purchase through the private sector, the equity of Canadian health care systems would be compromised. In addition, uncontrolled private sector involvement could result in the introduction of technically unsound or inappropriate technologies and services. To ensure adequate standards, it is important that appropriate guidelines and mechanisms for provincial licensing and monitoring of facilities and services be in place. These guidelines and mechanisms should apply to both the private and the public sector.

Role of Non-Governmental Organizations

Non-governmental organizations play an important role in Canadian health care.

Non-governmental organizations (NGOs), which represent individuals and address problems related to specific disorders, have an important role in Canadian health care. These groups, such as the Huntington Society of Canada, the Canadian Cystic Fibrosis Foundation, and the Multiple Sclerosis Society of Canada, provide funding for research, are strong advocates in their dealings with health ministries and professional organizations, and offer services relevant to specific disorders. Many NGOs provide excellent social and psychological help to individuals and families with genetic diseases.

The NGOs have identified a need for more genetics-related research and health services.

Canadians for Health Research, a voluntary association, recently surveyed 47 of these organizations, representing 185 000 citizens, for their views on available services and related needs in the area of genetic disease.[95] The survey results identified the need for more genetics-related research and health services (see Box 20).

Together, the NGOs represent a large, informed constituency of researchers, individuals with genetic diseases, and health care advocates with the ability to have a significant impact on health care policy.

5. ETHICAL AND LEGAL CONCERNS

Innovations and change create both opportunities and problems. This report does not identify all the ethical and legal problems arising from the application of genetics to health care, nor does it suggest how to resolve all those that are identified. It does attempt to demonstrate the range and importance of these issues, and it argues for the need to address them in the development and planning of genetic technologies and health services. We recognize that much work has already been done and is ongoing to identify and resolve ethical issues in genetics.[96] However, much still remains to be done.

Consideration of ethical issues should be integrated into development of genetic technologies and planning of services.

The issues surrounding human genetics will be difficult to distil into public policy for several reasons. The issues are complex and involve inherent conflicts. Attitudes toward many of the issues reflect the diversity of opinions and values among Canadians. There is no public consensus (and there may never be consensus) on issues such as prenatal diagnosis and termination of affected fetuses, or uses of genetic information. Any policies must accommodate a range of opinions.

The issues are complex, and there is often diversity of opinion.

But it is clear that genetic issues worry people. Serious concerns include:

- the potential for harm resulting from genetic engineering, including the ramifications of tampering with our essential "humanness";
- the possibility that information on personal risk of disease might be used to one's disadvantage; and
- the possibility that past eugenic abuses might be repeated, that genetic knowledge could again be used to justify claims of superiority or inferiority of races, or to discriminate against individuals.

Genetics deals with uncomfortable issues: genetic engineering, use of information, and possible eugenic abuses.

Genetic technologies can provide information about each of us, about our individual susceptibilities. Increasingly, our susceptibility to diseases can be diagnosed or predicted before we are able to use the information for our personal benefit. Moreover, we are accustomed to thinking of disease as an "outside enemy." The concept of genetic disease as an "internal" problem, resulting in part from our individual genetic make-up, requires us to change our thinking about disease.

On the one hand, not to apply genetics in health care will result in failure to develop and deliver many services beneficial to individual Canadians. On the other hand, failure to recognize relevant ethical issues may lead to inappropriate uses of genetic technologies and information. No satisfactory policies will emerge if public concerns about genetics in health care are not addressed. A process is needed to articulate these concerns, and the associated values and conflicts, and to work toward policies that allow a range of choices acceptable to most Canadians. If satisfactory policies are not developed, a backlash to the use of genetic technologies and health services may result.

No satisfactory policy will emerge until public concerns are addressed.

This chapter provides a brief overview of specific ethical issues associated with genetic knowledge, technologies, and health services.

Use of Genetic Technologies

The way in which genetic technologies will evolve and be applied will both affect and be affected by our social and moral structures. It is the view of the Science Council that the following principles must guide development and delivery of genetic technologies.

Genetic technologies should be available to treat or prevent genetic disease — not to improve the species.

- The primary objective of genetic applications in health care is to treat or prevent genetic disorders, not to reduce the cost of health care (although that may be an auxiliary benefit). Improving the human species is not an objective.

Genetic services should remain a voluntary option for individuals and families.

- Individuals and families should have access to beneficial technologies in order to make informed decisions about their own health care and reproductive options. The decisions should be based on reliable technical information and accurate, non-directive counselling. The individual's and family's decisions should be respected and supported.
- Genetic technologies should be used in the context of a caring society that values individuals and accepts human diversity and disability.

Individuals may choose not to avail themselves of genetic services. Participation is now, and should remain, a matter of free choice. Individuals should not be penalized (through reduced medical or social services, for example) for their reproductive or personal health care decisions.

Moral decisions regarding the use of genetic technologies should be made by individuals and society.

The "slippery slope" argument is often raised against the use of genetic technologies. The implication is that once initial steps are taken, there is no recognizable appropriate place to stop the use of genetic technology. The argument does not hold. Responsible distinctions can be made between a therapeutic application of a genetic technology, a trivial use, and the implementation of population eugenics. Moral decisions regarding the use of genetic technologies can and should be made by individuals and society.

Conflicts

Many ethical dilemmas result from differing interests and values.

Many of the ethical dilemmas associated with genetic knowledge and technologies arise from the conflicting interests of involved parties, conflicts between applications of competing ethical principles, and the range of opinion on specific issues. The involved parties include:

- individuals with genetic disorders or susceptibilities;
- their families;
- the fetus;
- society;
- future generations;
- geneticists and related researchers;
- health care delivery personnel;
- politicians and bureaucrats; and
- special interest groups.

The four basic principles of biomedical ethics are autonomy, beneficence, nonmaleficence, and justice.

The literature on biomedical ethics deals with the relationship of moral principles to rules and obligations, and is relevant to decision making regarding the applications of genetic technologies and information. The four basic principles of biomedical ethics are: autonomy, or respect for the wishes of competent persons; beneficence, or doing good; nonmaleficence, or doing no harm; and justice, or a fair distribution of benefits and harms. Related values include truthfulness, disclosing information to the patient, and confidentiality.

Among the areas of conflict to be resolved are:

- truthfulness versus perceived beneficence, in terms of disclosure of genetic information to patients;
- the interests of parents versus those of the fetus;
- the individual's right to confidentiality versus the information needs of family members at risk;
- the greater good of society versus the best interests of individuals;
- the interests of individuals alive today versus those of future generations; and
- the tension between the acceptance of disabled individuals and the provision of options to avoid birth of individuals with serious disabilities.

There are numerous areas of conflict to be resolved.

Accountability and Control

With genetic health care technologies changing rapidly, there is a growing need for accountability on the part of those involved in research, technology delivery, assessment of health care services, and use of information. But before the regulatory and legal system can address genetic issues, policies reflecting objectives and values are needed. The legal system should not be expected to set objectives and policies for genetic technologies.

Accountability is needed.

As noted by a Canadian expert in medical-legal issues:

> The approaches of ethics and of law to issues arising in medical care often result in conclusions which coincide, but the two disciplines are distinguishable, and their interaction merits attention. Both address questions of values, but the law must be constantly monitored to test whether it produces ethical effects.... One can identify circumstances, not only by reference to political oppression, in which the law may fail to protect significant ethical values.... There is an important sense in which law is a minimal ethic. When the law is not considered to be ethically deficient, its proper observance often discloses areas of unguided choice, where a legitimate discretion exists to act in different ways. The exercise of such discretion is a matter for ethical judgement and not for law.[97]

Genetic issues require both an ethical and a legal approach.

Some genetic issues — for example, the release of genetically engineered organisms into the environment, or access to medical information — are best served by regulatory control. However, most issues are best served by guidelines. Guidelines are more flexible and can result in more immediate and subtle responses to accumulating information and shifting social values. Guidelines have the further advantage of encouraging thoughtful decision making and assumption of responsibility. Awareness and understanding of ethical values is better achieved through the exercise of reasoned choice than through blind adherence to law.

Guidelines have advantages over regulations.

Finally, the setting of objectives for genetic technologies and the assessment of the need for guidelines or stronger regulatory instruments should be an ongoing process.

Box 21
Pre-Symptomatic Testing for Huntington Disease: Opinions of Three Individuals at Risk

"I think any at risk individual who wants the test should be able to have it. If he has been able to cope with the psychological hell of living at risk (and, believe me, it is hell), he should be able to cope with the knowledge he is carrying the gene. At least he can make plans for the future, whichever way the genetic dice have fallen."

"I consider it to be the height of irresponsibility on the part of doctors, lay groups, and even society to encourage the use of predictive testing to any at risk person no matter what this person says he wants to know, without an equally formidable medication that could offer hope. The repercussions will be staggering. If there's no hope, I say no test."

"Being at risk is a totally separate disease. Its symptoms and effects are far more widespread than HD is. It can limit or alter someone's entire adult life — not just the last 10 or 15 years. To free half the at risk people of both diseases in one test is worth it. More effective treatments cannot be far down the road."

Research

Scientists are responsible for ensuring the ethical conduct of research. They are also responsible for considering the effects of the potential applications of the research, and helping to set priorities and limitations.[98] However, it is not possible for scientists to anticipate all future uses of the information and related technologies.

Scientists are responsible for ensuring the ethical conduct of research.

Genetic research involving humans is subject to the same ethical considerations as other forms of medical research. The Science Council supports the Medical Research Council (MRC) guidelines for research involving human subjects (1987) and for research on gene therapy on humans (1990).[99]

Although the MRC guidelines address the issues thoroughly, only MRC-funded researchers are required to comply with them. (In addition, other research funding organizations, such as the Natural Sciences and Engineering Research Council, and some hospital research and ethics committees have chosen to adopt the guidelines.) There is a need to apply similar guidelines to all research involving gene therapy or experimentation with human subjects, irrespective of venue and funding. Local ethics review boards, already in place in hospitals, universities, and many private sector firms, could oversee compliance.

MRC guidelines are in place, but only MRC-funded researchers are required to comply with them.

Some issues associated with genetic research require additional or ongoing ethical and technical consideration. Such issues include the appropriate conditions for fetal research, use of fetal tissues, and anonymous testing for genetic diseases.

Genetic Health Services

Autonomy, counselling, informed consent, and confidentiality are the cornerstones of ethical delivery of genetic services. Some ethical issues related to genetic services have already been mentioned in previous chapters. Three major points:

Autonomy, counselling, informed consent, and confidentiality are the cornerstones of ethical delivery of genetic services.

- Genetic services should be initiated only if there are benefits such as disease prevention or treatment, or lifestyle or reproductive choices that can be made as a consequence. Opinions will vary on what constitutes a beneficial application (see Box 21).
- The importance of counselling individuals who are participating as subjects in human genetics research or in diagnosis and treatment programs should be recognized and accommodated.
- Follow-up health care and social support should be in place for individuals who have, or are at increased risk for, a genetic disorder.

Autonomy

The autonomy of individuals is a primary requirement in genetic services. Exceptions to this are children with serious diagnosable and treatable diseases, and mentally incompetent adults unable to make treatment decisions for themselves. For both groups, it must be demonstrable that the proposed services are in their best interests and improve their quality of life.

Autonomy of individuals is a basic requirement.

In the case of adolescents, genetic screening that conforms to recommended principles and practices has its advantages and benefits.[109] Adolescence is a period characterized by peer pressure and fragile self-image. Particular care is required in the conduct of such programs, and parental notification prior to screening is advisable.

Informed consent is fundamental to research and health care services.

The principle of informed consent is fundamental to all aspects of research and health care services. The consent of individuals should be obtained before undertaking research, conducting tests or treatments, releasing information on individuals, or before banking or using human tissues (including DNA).[110]

Prenatal Diagnosis and Pregnancy Termination

This report deals with the issue of pregnancy termination in a specific health care context. It does not address the wider issue of pregnancy termination: the rights of the fetus versus freedom of choice.

In cases of serious, untreatable genetic disorders, prenatal diagnosis and pregnancy termination should be valid health care options.

In the absence of effective disease prevention and treatment options, prenatal diagnosis of serious genetic disorders and pregnancy termination of affected fetuses should be valid health care options. The decision should rest with the individual woman. These diagnostic technologies are used primarily to help families at risk to have healthy children. Prenatal diagnosis should not be used to accommodate the preferences of parents on issues unrelated to serious health disorders (for example, to choose sex of offspring).[111]

These technologies help families at risk to have healthy children, but their use also implies value judgements on what kinds of life are worth living.

As more genetic conditions become detectable in the embryo or fetus, decisions will be required on which conditions are serious enough to warrant prenatal diagnosis. Some late-onset disorders or birth defects for which treatment is available (e.g., clinical depression or cleft palate) may be viewed differently by different families. The question remains as to who should make the decision whether societal resources should be used to make prenatal diagnosis available for such conditions. Ethicists recognize that individual and family decisions on pregnancy termination are in effect value judgements on what kinds of life are worth living.[112] These issues impinge upon our attitudes toward the disabled.

It should be kept in mind that prenatal diagnosis, although an important genetic service, does not contribute significantly to the number of pregnancy terminations. In 1984, for example, British Columbia had the highest pregnancy termination rate in Canada with 11 449 terminations and 43 911 live births; only 35 of these terminations were related to genetic problems diagnosed in the fetus. During 1984 almost 2000 genetic prenatal evaluations were done in British Columbia; 2.5 per cent of the evaluations showed abnormalities to be present.[113]

The search for better treatments must continue, even when effective prenatal diagnosis is possible.

The Science Council recognizes that the goal of genetics in health care is both to prevent disease and improve care. Therefore, the search for better treatment of genetic disease should continue, even for diseases where effective prenatal diagnosis is possible.

Responsibility and Liability

The physician has a general duty to know what a "reasonable" practitioner would know and to provide an acceptable standard of care. Provincial licensing bodies expect, and some require, that a physician keep up to date in knowledge.

This responsibility should extend to the delivery of services for dealing with genetic disease and susceptibility.[105] In other words, physicians should recognize the indications of genetic disease in individuals and families, incorporate appropriate diagnostic and treatment technologies into their practices, and refer patients and families to specialty genetic services as appropriate. For example, individuals at risk for familial bowel or breast cancer should be advised of precautions they should take to reduce their risk, and should be carefully monitored for early signs of disease.

The physician's responsibility to meet an acceptable standard of knowledge and care extends to dealing with genetic disease and susceptibility.

The issues surrounding prenatal diagnosis and pregnancy termination highlight the responsibilities of physicians and parents. Improved prenatal care and diagnostic technologies increase the responsibility and potential legal liability of those involved. The ethical and legal responsibilities of physicians and parents to the fetus are emotional, hotly debated issues.

Issues surrounding prenatal diagnosis highlight the responsibilities of physicians and parents.

In most contexts, the fetus is not afforded the legal rights of a person.[106] Therefore, it would seem that the wishes of the parents, and more specifically the woman carrying the fetus, generally take precedence in issues regarding *in utero* treatment and care. There is no legal obligation for a woman to accept *in utero* treatment.[107] This is not to say that parents do not have moral obligations. A woman carrying a fetus has a moral obligation to avoid wilfully harming the fetus through, for example, drug or alcohol abuse. However, she has no obligation either to carry a fetus to term or to terminate a pregnancy involving a disabled fetus. In this, as in other issues, the route to responsible, caring behaviour is through education and development of an ethical perspective, not through legal enforcement. There should be greater opportunity for education and counselling to ensure that prospective parents understand the effects of their lifestyles and choices on the unborn.

Physicians have a responsibility to advise parents on the health and health risks of the fetus, and on available diagnostic tests, the reliability of the tests, and the risks associated with testing procedures. A physician has the duty to advise clients as to the availability of these services, even if he or she does not agree with their use for technical or ethical reasons. Failure to inform is not responsible medical practice. In the United States, parents have launched "wrongful birth" court actions against physicians who failed to detect fetal abnormalities or advise the parents in sufficient time to offer the option of terminating the pregnancy.[108] However, a child born with such abnormalities has no legal grounds for claiming "wrongful life" against parents or physicians. The courts consider that a legal right not to be born would be a violation of the sanctity of human life.[109]

Physicians should advise clients of available carrier and prenatal diagnostic services.

Negligent, incorrect carrier testing of parents prior to conception and subsequent birth of a handicapped child is again actionable by the parents.[110] In these cases, judgements offering compensation to the child are now appearing. Compensation is based on restitution for pain and suffering rather than on the right not to be born.[111]

Information

The information that genetic technologies provide about an individual's risk for disease can be harmful as well as helpful. If misunderstood or misused, genetic information can result in unfair discrimination. Moreover, genetic information, even if used legitimately, could disadvantage individuals with or at high risk for

Genetic information can be harmful as well as helpful.

specific disorders, for example through exclusion from employment opportunities or insurance coverage.

Policies and action are needed to prevent misuse of genetic information.

There is a need to determine the desirable and acceptable uses of information on genetic disease or susceptibility, and a need for policies and action to control access to, and prevent misuse of, such information. Similarly, policies and action are needed to help individuals disadvantaged in some way because of knowledge about their genetic make-up.

Counselling and education are the essential partners of genetic information. Counselling helps individuals deal with their personal risk of disease; education helps individuals understand the implications of disease susceptibility for society, and creates acceptance and support of the disabled.

Genetic information should not be used to promote racist or discriminatory policies.

Genetic information should not be used to establish or promote racist or discriminatory policies. Genetic differences between individuals and between races and populations are normal, and genetics affects many aspects of human biology and behaviour; however, there is no evidence for the "inferiority" or "superiority" of one race over another. All races encompass a range of capabilities; the differences between individuals within races greatly exceed the differences between races. Moreover, behavioural traits are clearly the product of both environmental influences and genetic endowment.[112] Society's goal should be to assist all individuals to achieve their maximum potential.

Guidelines and, where necessary, legal instruments should be used to ensure the rights of individuals. The existing Charter of Rights and Freedoms and provincial human rights legislation are likely to be sufficient to protect individuals from discrimination on the basis of genetic knowledge.[113]

As a priority, the current and potential uses of genetic information should be reviewed with the objective of identifying possible problems and developing policies and controls. Issues to be considered include insurance and workplace access to information, disease registries, and DNA banks.

Confidentiality

Conflicts relating to the confidentiality of patient information can arise when disclosure could benefit other family members.

All personal medical information, including genetic information, is confidential. In the classic medical model, the individual with the symptoms is clearly the client, the person whose interests the physician must serve. But a potential conflict arises when information about one member of a family could be used to benefit other family members. Genetic diagnostic technology frequently produces information that could be beneficial to other family members since they share a common genetic heritage.

Counselling and public education on genetic diversity should gradually reduce the number of individuals who do not wish to share such information. However, if an individual remains unwilling to divulge information that could significantly affect the health or reproductive choices of other family members, the physician may still transmit the relevant information under certain circumstances:

The duty of confidentiality to an immediate patient can be overridden under certain circumstances.

A professional's ethical duty of confidentiality to an immediate patient or client can be overriden only if several conditions are satisfied:
(1) reasonable efforts to elicit voluntary consent to disclosure have failed;
(2) there is a high probability both that harm will occur if the information

is withheld and that the disclosed information will actually be used to avert harm; (3) the harm that identifiable individuals would suffer would be serious; and (4) appropriate precautions are taken to ensure that only the genetic information needed for diagnosis and/or treatment of the disease in question is disclosed.[114]

These principles should be integrated into delivery of genetic health services in Canada.

Full Disclosure

Full disclosure of medical information to the patient is an appropriate objective. Yet an international survey of medical geneticists that addressed this topic and other counselling dilemmas demonstrates the complexity of the issues and the variation in attitudes among counsellors and cultures (see Box 22). For many geneticists there are circumstances where providing only the information required to ensure appropriate health benefits is preferable to providing the full truth.

Full disclosure of medical information to the patient is an appropriate objective, but not always considered the best course.

Prior to genetic testing, individuals and families should be informed that tests can reveal non-paternity, or the presence of disorders or disease susceptibilities unrelated to the original investigation. The question of whether such information is to be transmitted to the individual and to the family should be discussed and agreed upon in advance.

DNA Banking and Registries

DNA banking and disease registries will be of particular significance over the next few decades. Banked genetic material can be used for a multitude of research and diagnostic purposes including storage awaiting future technology, linkage analysis, genetic diagnosis, retesting using new technology, and sharing of material among genetic centres.

Genetic banks and registries facilitate patient services and advance research.

The establishment of banks and registries should be encouraged. But in conjunction with their development, it is essential that appropriate protocols be followed to ensure the consent and confidentiality of the individuals involved, and to ensure that participants understand the potential uses of the banked material and specify the uses to which they consent.[115] It should be made clear that individuals have full control over their level of participation, and that they can decline any or all participation without affecting their future access to improved clinical diagnosis or treatment. Appropriate operating procedures for DNA banking have been identified.[116]

Appropriate protocols to ensure confidentiality should be in place.

Property Rights

The potential commercial value of DNA material and of products derived from human tissues has led to debate (and lawsuits in the United States) over the rights of individuals to share in profits accruing from use of their tissues.[117] Are genes and genetic material "property"? What are the rights of the person who is the source of the material?

Box 22
Full Disclosure of Sensitive Information

Genetic testing can result in psychologically sensitive information that may harm the patient or family members. Should there always be full disclosure? The decisions involve a balance between the physician's duty to tell the truth (the patient's right to know) and the duty to do no harm.

The following examples from an international survey show how clinical geneticists in general, and Canadian geneticists in particular, handle these issues.

Problem 1:
Genetic testing has revealed which parent carries an abnormality (balanced translocation) that has caused Down syndrome in their child. Disclosure might enable the couple and relatives to use reproductive options to prevent the birth of another Down syndrome child. But the knowledge could also cause guilt in the carrier, and perhaps threaten the marriage.

How do geneticists handle this dilemma?
Fifty-four per cent of survey respondents (60 per cent in Canada) would disclose which parent is the carrier. An additional 43 per cent (40 per cent in Canada) would tell the couple that the information exists and give them the option of knowing.

Problem 2:
A woman is investigated for infertility. The investigation reveals that she has an XY (male) genetic make-up. Full disclosure could damage her self-image, but would resolve doubts about fertility.

How do geneticists handle this dilemma?
Fifty-one per cent of survey respondents (68 per cent in Canada) would disclose the XY status. The remaining 32 per cent of Canadian respondents, while offering an explanation of her infertility, would avoid full disclosure.

Problem 3:
During evaluation of a child with an autosomal recessive disorder, for purposes of genetic counselling, it is discovered that the husband is not the child's biological father.

How do geneticists handle this dilemma?
For 96 per cent of survey respondents (96 per cent in Canada) protection of the mother's confidentiality overrides disclosure of true paternity. Eighty-one per cent (87 per cent in Canada) would tell the mother in private. The primary reason given for not informing the husband was "preserving the family unit."

Problem 4:
Repeated maternal serum alpha-feoprotein (AFP) tests of a patient are below the norm. Some studies have found low AFP values to be associated with Down syndrome, but geneticists do not agree on the interpretation of low values.

How do geneticists handle this dilemma?
Eighty-two per cent of survey respondents (94 per cent in Canada) would tell the patient that geneticists are not in agreement, but there may be a possibility of Down syndrome; they would discuss the risk of genetic abnormality, discuss the option and risk of prenatal diagnosis, and let the patient decide whether to use prenatal diagnosis.

It is not clear whether genetic material would qualify as personal property under Canadian law. The full range of ethical issues and available legal mechanisms warrant detailed consideration. For example, even if genetic material were deemed property, the donor's claim in any commercial profits might be limited to the value of the tissues when they were removed (i.e., the value before research or processing into the final commercial product). Such value would be extremely difficult to determine.

Whether or not an individual's genetic material is "personal property," it should not be sold...

The debate over whether genetic material is property should not be allowed to undermine the current Canadian philosophy of gift-based donorship; extension of the donor philosophy would mean that genetic material could not be sold, and donors would not have commercial interest in products developed using their tissues. However, it is critical that in all cases individuals have control over the use of their tissues, including use in research or in the development of commercial products. Consent should be obtained prior to conducting research using genetic material, even on tissues removed for diagnostic or therapeutic purposes and considered to be "abandoned."

...but in all cases the individual should have control over use of the material.

Eugenics

There are several definitions of eugenics:

- "The science which has for its object the production of fine offspring, especially in the human race."[118]
- "A term coined by Galton to denote practices and policies that tend to better the innate qualities of man and to develop them to the highest degree."[119]
- "A strategy of trying to orchestrate human evolution through programs aimed at encouraging the transmission of 'desirable' traits and discouraging the transmission of 'undesirable' ones."[120]
- "Any effort to interfere with individuals' procreative choices in order to achieve a societal goal."[121]

Population eugenics was practised in this century, not just in Nazi Germany, but in different ways and to varying degrees in many countries, including Canada.[122] In Canada, eugenics was practised through sterilization of the "unfit" and certain immigration policies and practices (see Box 23). These official practices no longer exist. They were due to a combination of poor science, subversion of science to meet social objectives, and a disregard for basic human rights and ethical principles. The past abuses account for part of the public and political unease in addressing genetics and eugenics issues. However, medical geneticists in Canada today are clearly oriented toward individual and family needs and are not primarily concerned with the impact of parental reproductive choice on society, let alone the human species. Thus:

Eugenics was practised in many countries, including Canada.

Medical genetics as practised today focuses on the needs of individuals and families.

> Medical geneticists in Canada and in other countries may vehemently and correctly reject any...link between their work and the reprehensible eugenic programmes of the 1930s and 1940s.... Vehement rejection of eugenic charges may not suffice over the next decade as the power of diagnostic technology increases. Medical geneticists and others may well have to engage themselves more explicitly than ever before in methodological and interdisciplinary reflection on the history of genetics and on the future course of genetics in an evolving society.[123]

Box 23
Historical Examples of Eugenics in Canada

Canadian eugenicists of the early 20th century believed the nation had to be protected against the racial degeneration (physical and mental) of its population. They attempted to influence policy development and legislation concerning control of reproduction among the "unfit" and restrictions on immigration.

Control of Reproduction

1912 A bill was presented to the Ontario legislature allowing sterilization of asylum inmates declared unfit to marry and produce children. Lack of public support for the bill induced its withdrawal.

1917 The Ontario government appointed a Royal Commission on the Care and Control of the Mentally Defective and Feeble-Minded. Its report of 1917 included restriction of marriage among its recommendations. World War I diverted attention from the report's findings.

1925 A Royal Commission on Mental Hygiene was appointed by the British Columbia government. The Commission's final report, issued in 1928, recommended sterilization as a policy option. It argued that sterilization would prevent the feeble-minded from passing their affliction on to their children. No immediate action followed the Commission's recommendations but they paved the way for later legislation.

1928 The United Farmers of Alberta government passed the Sexual Sterilization Act with the full support of organizations such as the United Farm Women of Alberta, the Imperial Order of the Daughters of the Empire, and the Women's Christian Temperance Union. Under the Act, the institutionalized mentally ill could be sterilized if this was approved by a Eugenics Board and consent was obtained from the patient or guardian. In 1937 the consent provision was removed.

1929 Ontario's Royal Commission on Public Welfare recommended that a policy of compulsory sterilization be adopted to decrease the numbers of the feeble-minded. Again the recommendations were not adopted by the government.

1933 The Conservative government of British Columbia passed the Sexual Sterilization Act with little opposition. Superintendents of relevant institutions could apply for approval of sterilizations to a Board of Eugenics. The Act applied to persons "likely to beget or bear children who by reason of inheritance would have a tendency to serious mental disease or mental deficiency." Consent was required from the inmate if capable, otherwise from the spouse, guardian, or Provincial Secretary.

1938 Ontario's Royal Commission on the Operation of the Mental Health Act recommended a sterilization policy. The Ontario government refused to act once more, partly because of personal opposition from the deputy minister of health and partly because the province's Roman Catholic minority opposed sterilization.

1972 The Sexual Sterilization Acts of Alberta and British Columbia were repealed.

Outcome

Between 1928 and 1971, 2822 cases were approved for sterilization in Alberta. No records remain for British Columbia, but the number of mentally ill and mentally deficient persons sterilized was probably in the order of a few hundred.

(continued on page 78)

The Science Council wishes to emphasize the following points.

- Genetic technologies should be used voluntarily; they should not be applied as an enforced form of population eugenics.
- There must be back-up health care services for individuals who do not, or cannot, avail themselves of available services to prevent, avoid, or treat genetic diseases.
- Genetic services and back-up health care services should be publicly funded, or a social and economic bias will result. For example, if publicly funded health services are not available for disabled children, there is an implicit economic pressure on lower-income families to avoid the birth of such children through prenatal diagnosis and pregnancy termination.
- We must ensure that availability of genetic services does not decrease our acceptance of the disabled.

Genetic technologies should not be applied as an enforced form of population eugenics.

Non-Medical Applications

Genetic technologies are used for purposes other than health care. Two major applications (workplace and insurance testing) are discussed separately here. Other potential non-medical uses include: to select the sex of offspring,[124] to prove kinship or paternity for legal or immigration purposes,[125] to conduct forensic investigations,[126] to develop agents for biological warfare (including agents effective on specific ethnic groups),[127] and to assess prospective immigrants for diseases or susceptibilities that could impose burdens on the health care system.

Non-medical applications of genetic technology include forensic investigations and biological warfare.

To prevent undesirable uses, all proposed applications should be subjected to technical and ethical review and to policies and regulatory instruments as appropriate.

Workplace Applications

Workplace screening is a one-time test of individuals, prior to employment, to determine whether they have genetic susceptibilities that would predispose them to occupational disease. Genetic monitoring entails periodic testing of employees to discover any genetic damage resulting from exposure to workplace mutagens.[128]

Genetic screening or monitoring programs can be beneficial if used to create a healthier work environment or to relocate high-risk individuals to safer jobs. But such programs could be considered discriminatory and in violation of workers' rights to security, integrity, and privacy if they are used to exclude or dismiss individuals from employment when the specific risk of disease is unrelated to workplace conditions or requirements.[129]

Genetic screening and monitoring programs have the potential to be used to the benefit or the disadvantage of employees.

Genetic screening in the workplace has been applied in the United States for more than 20 years. Although applications remain limited, employer interest is considerable.[130] But in the past, there have been some abuses and some misunderstanding of the risks of specific disorders. For example, individuals who were carriers of sickle cell gene were in many cases treated, incorrectly, as though they were sufferers of the disease and excluded from employment opportunities.[131]

Workplace applications of genetic screening remain limited, but there is considerable employer interest.

Box 23 (continued)

Although there was no enabling legislation, sterilizations of the mentally retarded were performed in Ontario. Sterilizations were clearly performed more frequently on specific groups. For example, during the last few years of the legislation's existence in Alberta over 25 per cent of sterilizations were carried out on Indians and Métis. These groups represented only 2.5 per cent of the Alberta population. There is no evidence that sterilization had any effect on the overall frequency of mental "deficiency."

Immigration Restrictions

1869 Canada's first Immigration Act prohibited the entry of "lunatics" and "idiots."

1901 Medical inspections were initiated at Canada's borders.

1910 A new Immigration Act divided undesirable immigrants into three major categories: mental defectives (including epileptics, idiots, the feeble-minded, imbeciles, and the insane); physical defectives (including the dumb and blind); and people with "loathsome" diseases or those deemed a risk to public health.

1928 By this time, the Department of Immigration was employing 28 medical examiners across Britain and the rest of Europe to screen immigrants and exclude unsuitable candidates.

1928 A federal Select Committee on Agriculture and Colonization submitted a report calling for stricter controls on immigration. The "hereditary deficiencies" of immigrant groups were an integral part of the discussions preceding the report. Stricter immigration controls were subsequently introduced but mostly as a result of the Depression rather than eugenic concerns.

Outcome

During the 1920s about 10 000 people were excluded from immigration to Canada for health reasons.

In Canada, employment law and the statutory and constitutional protection of individual rights are pertinent to genetic screening and monitoring in the workplace.[132] Following are items of particular relevance.

Employment law and statutory and constitutional protection of individual rights are pertinent.

- An employer is allowed to assess the skill, training, and medical status of a job candidate in relation to a specific job. Other than for positions that involve public safety (e.g., commercial airline pilots), the employer is not considered to be under a duty to determine if the potential employee is generally medically fit for the work.[133]
- Federal and provincial occupational health and safety statutes make employers responsible for ensuring the health and safety of their employees on the job. This responsibility makes it possible, perhaps even obligatory, for employers to establish genetic screening and monitoring programs.[134]
- Non-employment of genetically susceptible applicants or redeployment of susceptible employees should not be used as a substitute for improving the work environment.[135]

Genetic screening is not a substitute for improving the work environment.

- An employer may impose "reasonable" screening tests on job applicants, that is, tests that are scientifically valid, reliable, and related to the job in question. The applicant can comply or withdraw the application. The rights of established employees with regard to genetic screening and monitoring are bound up in contract law and more complicated.[136] All these issues will probably be tested in Canadian courts within the decade.
- Exclusion from employment on the basis of genetic susceptibility may be considered discrimination based on handicap or disability. However, exclusion from employment may be permissible if the employer can show that the employee is unable or likely to be unable to substantially meet the essential requirements of the job because of the susceptibility, or can demonstrate that the susceptibility results in an unacceptable degree of risk for the employee, fellow workers, or the public.[137] It is not yet clear what kinds of risk are unacceptable or what kind of evidence is necessary.

Genetic susceptibility is not necessarily reasonable grounds for exclusion from employment.

- In some provinces employers have a responsibility to provide susceptible employees with alternative, safer employment (at equal pay).
- Finally, it should be remembered that every individual carries some form of genetic-based susceptibility to disease. However, that susceptibility may never express itself in disease.

These issues point to the need to determine how genetic screening and monitoring should be used in the Canadian workplace, and then to ensure that appropriate legislation is in place.

Life and Disability Insurance

The application of reliable genetic diagnostic technologies has implications for the life and disability insurance industry and for individual Canadians.[138] At present, some disability income is provided by provincial governments and is available to all Canadians who qualify. In addition, many Canadians are covered by group or individual life and disability insurance policies offered by private firms or cooperatives. The purchase of life or disability insurance is not obligatory, and the right to buy such insurance is not guaranteed. Insurance is a contract and depends on good faith between the insurer and the person insured.

The application of genetic technologies in the current system of individually purchased life and disability insurance would allow an insurance company to set premiums that realistically reflected risk and to identify and avoid insuring individuals who were poor risks. The information would benefit individuals

Use of genetic screening for insurance purposes could result in a growing number of individuals deemed to be uninsurable.

who received a relatively clean genetic bill of health, but as diagnostic technologies became increasingly available would also result in a growing number of uninsurable individuals or, at best, individuals penalized for their personal biology.

Insurance companies are interested in identifying higher-risk individuals; however, applying genetic testing technologies is at present too complicated and expensive to have a major impact on the insurance industry. Still, some individuals with specific knowledge regarding their genetic health status do stand to be penalized.

There is a need to review options for providing life and disability insurance to such individuals.

Therefore, the time is now appropriate for a review of the insurance issues and alternatives. Is the purchase of life and disability insurance a "right," and if so how much should everyone have the right to purchase? What medical information should insurance companies have the right to request? How should insurance of high-risk individuals be accommodated? The options include "no-fault insurance," which averages out the risk and expense over the population; development of special high-risk insurance pools; or some form of basic insurance universally available at the same premium, with purchase of additional insurance optional and contingent on genetic information.

Representatives from the life and health insurance industry, consumer groups, and relevant government agencies should consider conducting a joint review to address the implications of emerging genetic information and technologies on life and disability insurance.

6. EDUCATION AND AWARENESS

Until genetic knowledge and technologies are appropriately integrated into our health care systems, Canadians will not fully achieve the related benefits in disease prevention and treatment. To better realize the benefits of genetic technologies and to avoid their misuse, the Canadian public, health care professionals, and health policy makers need to become more aware of what the technologies and services can (and cannot) accomplish. This awareness should be anchored in solid scientific education and nurtured through full and open discussion of the issues.

Canadians need to become more aware of the potential of genetic technologies and services.

The education of most adult Canadians has not prepared us to deal with the issues that affect our health and our health care systems. Although Canadians generally have a high interest in health issues, most of us lack fundamental knowledge in biology and the health sciences, and we have little understanding of the biological mechanisms that affect personal health and the specific factors that place it at risk. Instead, we depend on information and direction from health care providers. Our ignorance does not confer bliss. On the one hand, we have an unrealistic expectation of what curative medical technologies can accomplish; on the other hand, we are resentful of surrendering control to high-technology health care that is seen as growing increasingly impersonal.

Most Canadians lack fundamental general knowledge in biology and the health sciences.

Individual Canadians need to acquire the basic knowledge necessary for them to play a greater role in understanding and managing their health and to participate in the debate on future directions for their health care systems. Only then can the users and the providers of health care become full partners. To achieve this, there is a critical need for better public education about health and health care. A knowledge of genetics and human diversity is increasingly a necessary part of understanding the determinants of health.

Individual Canadians should play a greater part in understanding and managing their health.

To address genetic issues adequately, the education process has to begin in elementary school and be carried on through our secondary schools, universities, and education programs for health care professionals. But education is a lifelong process and must also reach those in the general public and health care community who have already completed their formal schooling.

The education process must begin in the elementary grades and continue throughout life.

Elementary and Secondary Education

All Canadians should leave the public school system with a basic understanding of the important human biology (including genetic), environmental, lifestyle, and health care factors that affect health. This knowledge would serve as a framework to help individuals maintain their own health, and to understand the changes in health sciences and technologies that will occur during their lives. At present, most Canadians do not leave the school system with this knowledge. This is part of a larger problem: the inadequacy of science education in Canada, which was the subject of an earlier Science Council report.[139]

The climate for science and health education is improving. The current trend in science education is toward practical applications of science and the role of science in the lives of citizens. Attention is now being focused on the social context of science, as well as on scientific information and skills.[140] The health and social applications of genetic science and technologies are a logical component of this approach.

The climate for health education is improving, but some problems remain.

Science and the associated health issues are usually not well integrated in our schools.

Some problems still remain in providing genetic information to students. Although modern research is breaking down the barriers between formerly distinct disciplines, science and associated health issues are usually not well integrated in our schools; biology and health, for instance, are frequently taught in separate courses. Often the connections are not made between scientific facts and principles, human health, health care technologies and applications, and related social issues.

In addition, there are problems in developing and delivering an effective curriculum.[141] The teaching of genetics can be considered in terms of:

Genetics can be considered in terms of the intended, planned, taught, and learned curricula.

- the *intended* curriculum, defined by the curriculum outlines prescribed by the provincial ministries of education;
- the *planned* curriculum, consisting of programs and lesson plans created at the school board, school, and teacher level;
- the *taught* curriculum, which is what the students actually experience through classroom discussions and workbooks; and
- the *learned* curriculum, which is defined by the students' intellectual and practical achievements.

The health and science curricula up to Grade 9 provide little material on human genetics.

At present, the health and science curricula up to Grade 9 provide little material on human genetics or on the relationship between genes and health. In the upper grades, revised biology curricula are starting to reflect advances in genetic science. However, by Grade 10 many students have dropped out of school or have opted not to take biology; less than a quarter in the 15- to 19-year age group enrol in biology courses.[142] Therefore, the majority of students receive little instruction on the role genes play in health and disease.

Genetic knowledge and related health issues are developing rapidly and are not adequately represented in older curricula.

Significant findings on the role of human genetics in health have not been incorporated into most provincial curriculum objectives or school board outlines. In theory, curriculum reviews are to be conducted every five to eight years. In practice, intervals of 15 years are more common. The oldest existing biology curriculum, in Saskatchewan, was developed in 1971 (it is currently under revision); the most recent, in Ontario, dates from 1987. Genetic knowledge and related health care issues are developing rapidly and are therefore not adequately represented in the older curricula.

The current curriculum outlines for advanced biology courses generally cover theoretical aspects of genetics such as Mendel's laws, mitosis, meiosis, protein synthesis, and DNA replication. Curricula rarely cover the concept of genetic susceptibility to disease, or applications of genetic knowledge such as screening and counselling, or the associated ethical and social issues. There are exceptions. The advanced biology curricula in Ontario and Manitoba are excellent, not simply on the basis of their scientific content but also in their consideration of health implications and applications. In both provinces the medical genetics community assisted in the development of the curriculum.

The scarcity of textbooks and other teaching aids for genetics is particularly a problem.

Even when the health implications of genetics appear in the curriculum outline, the topics may not be included in the planned and taught curriculum. Course preparation is hampered by a lack of suitable textbooks (especially Canadian textbooks) and teaching aids. The Canadian market for textbooks is small and therefore publishers are generally slow to respond to changes in knowledge and perspectives. It is possible that the new Ontario and Manitoba biology curricula will result in the publication of Canadian biology texts that effectively cover genetic issues. The scarcity of textbooks and other teaching

aids is particularly a problem because genetic knowledge and issues are relatively new and teachers are unlikely to have received related formal training.

Biology teachers indicate that they generally do not teach health and social issues associated with genetics because they lack the information and resources necessary to cover the topic.[143] However, the teachers are interested in the issues and there is also evidence of student interest.[144] It is noteworthy that some excellent courses are being delivered in areas where local medical genetics centres have provided resource materials and professional development programs for teachers. More contact between teachers and the medical genetics community would assist in integrating genetics into the planned and taught curriculum.[145]

Teachers generally lack the information and resources to cover the topic.

More interaction between teachers and the medical genetics community would help integrate genetics into the curriculum.

To reach all students, the teaching of the fundamentals of human biology, genetics, and health should begin in elementary school and be a part of the core curriculum in junior high school. Courses should integrate the science and health aspects of genetics; students should also be introduced to the social and ethical choices that health applications raise.[146]

Although education is a provincial responsibility, in this era of rapid scientific advances it would be inefficient and time-consuming for each province to upgrade its curriculum on its own. Educators and students would both benefit if a national clearing house or agency, such as the National Association for School Health, were charged with providing up-to-date course outlines on biology and health that could be adapted by the individual provinces. Final responsibility for the curriculum would remain with the province, but the clearing house could serve as a resource, obtaining advice from the relevant health experts in developing the different units, producing teaching aids, and offering teaching clinics. The Canadian College of Medical Geneticists could provide ongoing curriculum advice to the clearing house.

A national clearing house or agency could provide provinces with course outlines and teaching aids.

University

Exposure to molecular biology and human genetics concepts at the undergraduate level could influence more science graduates to choose a related career or research specialty. Such exposure could also have direct applications for future health care workers, science teachers, and biotechnology entrepreneurs.

Exposure to human genetics at the undergraduate level would enhance the general knowledge of all science graduates.

General biology and molecular biology courses should provide information on the growing knowledge about, and technologies associated with, the mapping of the genome and the links between specific genes and diseases. Undergraduate biology programs should also introduce students both to the industrial and entrepreneurial opportunities associated with biology, and to the related social issues. To help achieve these goals, each biology department chairperson should undertake a curriculum review, and adjust the curriculum as needed.

Biology department chairpersons should review undergraduate curricula and make appropriate adjustments.

Public Education

Canadians would benefit from up-to-date information on health care issues relevant to their own personal well-being; they need information to improve their understanding of the social and technical issues surrounding Canadian

An informed public is necessary to ensure appropriate policies.

health care systems in general and genetic health care technologies and services in particular. In a democratic society, an informed public is essential for appropriate and effective decision making. The basic scientific literacy established through the formal education system must be supplemented and updated throughout life.

There are a number of ways to improve public awareness of health issues. These take advantage of the abilities and resources of government agencies, special interest groups, and the media.

For example, the *Ask Your Family Tree* readers' guide and workbook is a government-sponsored self-help health guide.[147] Its objective is to identify disorders for which family members (current and future) may be at risk. The guide helps in the construction of a three-generation family health tree, and provides basic information on the concepts of genetic disease and some common genetic disorders. The guide also identifies sources for additional information.

Federal and provincial health departments and non-governmental organizations could expand their role in public education.

In general, however, the federal and provincial health departments could expand their role in public education. The departments have the resources and experience to deliver excellent public education programs.

Professional and special interest groups such as the Canadian Medical Association, the Canadian College of Medical Geneticists, and various disease-specific associations also have important messages to deliver on the issues surrounding genetic knowledge and technologies. These organizations are making a valuable contribution by providing information needed for informed public debate.

Scientific literacy in Canada is poor.

There is still room to strengthen communications. Scientific literacy in Canada, as in Great Britain and the United States, is poor.[148] The Royal Society of Canada is addressing this problem by developing and promoting mechanisms for more effective communication of science and technology issues to the public.[149] Awareness of genetics-related issues would likely improve if provision of information to the public became a higher priority of the Canadian College of Medical Geneticists.

The public consistently expresses a strong interest in health care issues. The media provide coverage when information on genetic disease is packaged in an interesting and relevant manner, whether by government agencies, research institutes, scientists, or other experts in the field.

Health Care Professions

Until genetics is given a higher priority in the training of health care professionals, Canadians will not be able to reap all the benefits offered by the associated diagnostic and therapeutic techniques.

An understanding of the role of genetics in health is important to many health care fields.

An understanding of the importance of genetic predisposition to disease affects a range of health care fields including dentistry, dietetics, medicine, nursing, pharmacy, rehabilitation therapy, and social work. At present, genetics is poorly integrated into education in all these disciplines.[150] Provincial and national associations, accreditation bodies, and curriculum committees of the different health professions could address the problem by initiating a review of

the status of genetics education within their professional training with a view to modifying their training programs, objectives, and examinations as needed.

Education of Physicians

> We are now at a critical crossroads for the integration of human genetics teaching into medical school curricula.... Genetics is a core discipline in medicine that deals with human biological development and variation throughout the life cycle; hence, genetics is especially important in epidemiology and prevention of human disease. Molecular technology has provided human genetics with tools to begin to understand disease, within medical sub-specialties and across all age groups. As other fields begin to make use of this technology, human genetics can provide a central paradigm for the education of medical students.[151]

Genetics is not well integrated into medical education at all levels.

The applications of genetics to diagnosis, prevention, and treatment of a wide range of disorders are growing rapidly. However, many medical schools are not adequately preparing students to understand the revolution in human genetics that is affecting all areas of medicine. Although there are some promising signs of progress, genetic considerations are currently not well integrated into medical education at the undergraduate, specialty, or continuing education levels.[152]

A task force has identified a number of problems associated with teaching genetics in medical schools.

A 1985 survey of educators reported data from 119 of the 140 North American medical schools.[153] In 47 per cent of the schools, teaching of human genetics was assessed as nonexistent or poor. In 52 per cent of the schools, teaching of human genetics was the responsibility of the paediatrics department. The human genetics that was taught emphasized cytogenetics, Mendelian inheritance patterns, and clinical genetics. In many schools the basic science aspects of genetics were not covered at all; the gene was considered more as a heritable unit in a Mendelian sense than as a complex informational molecule. This perspective, although important, offers a limited view of genetics in health care and does not provide the necessary foundation for continuous, career-long learning.

A task force formed by the American Society of Human Genetics has examined and addressed the problems involved in teaching genetics in medical schools.[154] Some of their major findings appear in Box 24.

The challenge facing medical educators has not changed in more than a century — the overriding objective is still the preparation of competent and caring physicians. The central dilemma remains how to invest graduating physicians with a process for thinking about health and disease, instil a vast amount of factual knowledge, and prepare them for a lifetime of learning, all the while maintaining the humanity in medicine. The problem is aggravated today by tremendous growth in the factual material to be learned.

There are three components to incorporation of genetics into the curriculum.

Integration of medical genetics into the curriculum involves three approaches:

- as a basic science underlying all aspects of health and health care, with emphasis on the gene as a complex informational molecule;

Box 24
Teaching Genetics in North American Medical Schools

An American Society of Human Genetics task force found that the concepts of genetic disease and the benefits of genetic technologies have not been well integrated into undergraduate medical education. The task force noted:

- a lack of relevant teaching resources in many medical schools;
- a lack of vertical integration of human genetics teaching through all four years of medical school;
- a lack of a minimum core curriculum on human genetics;
- a need to teach students a genetic approach to thinking about clinical problems;
- a need for appropriate evaluation of the genetic knowledge of students;
- a need for an implementation strategy to improve teaching of human genetics.

There are several reasons why genetics has not been well integrated into medical education.

- The applications of genetic science are relatively new and still evolving.
- The importance of the new molecular biology knowledge and technologies in understanding and treating disease has not been adequately conveyed to the appropriate decision makers.
- Rapid advances in many other aspects of medical knowledge and technology are resulting in strong competition for curriculum content.
- In setting the curriculum and teaching, medical school faculty place priority on what they personally know to be important. Most faculty were educated before the current proliferation of genetic information.
- Health care educators with in-depth medical genetics training are rare.

- as a specific course on "medical genetics," with topics ranging from the basic science of genetics and the role of genetic variation in health and disease, to clinical medical genetics and ethical and legal issues;
- as an integral component of all other courses: biochemistry, cell biology, cardiology, neurology, and so forth.

In addition, the new medical technologies, including genetic technologies, are raising ethical dilemmas and concerns about misuse. The training in medical ethics that physicians receive should be designed to help them address the related issues in genetics.

Training in medical ethics should help physicians in addressing related issues in genetics.

The ultimate objective is to provide students with a broad conceptual framework regarding genetic mechanisms and applications and to instil a "genetic way of thinking." Medical education can involve different approaches including lectures, tutorials, formal courses, and training centred on case studies. The integration of genetics can be adapted to all these approaches.[155]

The objective is to instil a "genetic way of thinking."

Educators need help to keep up with progress in genetic knowledge. One development from which Canada may benefit is the program the American Society of Human Genetics (ASHG) has established, with Canadian input, to monitor and assist in improving the teaching of human genetics. The program will develop and provide educational resources, help to educate ASHG members in teaching methods, and encourage evaluation of human genetics education and learning.[156] The development of teaching aids is a priority: textbooks, monographs, slides, videos, and case studies for small group discussions are all required. Also considered a priority is a clearing house to provide information on the available resources.

The ASHG task force that reviewed medical education in North America concluded that the examination questions used to evaluate the genetic knowledge of medical students assessed a "primitive level of learning." The task force called for development of a bank of appropriate questions and answers.[157]

The growth in genetics knowledge also has implications for postgraduate medical education. Medical genetics has only recently been accepted as a freestanding specialty by the Royal College of Physicians and Surgeons of Canada. The new specialty training program should result in the availability of more providers of genetics-related health care and should heighten awareness of the importance of medical genetics among other health care professionals, resulting in a better integration of genetics into general health care delivery.

Medical genetics is now accepted as a freestanding specialty by the Royal College of Physicians and Surgeons.

As in undergraduate medical education, it is crucial that the role of genetics in medicine not be considered uniquely the territory of medical geneticists. A review of the Royal College's specialty objectives and examinations shows that genetic considerations are not well integrated into other relevant specialty programs.[158] Genetics questions on the specialty exams focus largely on the rare, classic disorders and their diagnosis. Generally, the exams do not reflect advances in genetic science and knowledge, or the relevance of genetics to common diseases and disease prevention. The integration of genetic considerations into the different specialty programs could be improved if each Royal College specialty committee consulted with a medical geneticist familiar with that specialty and then adjusted its objectives and examinations to reflect current genetic knowledge and relevant applications.

Integration of genetic considerations into other postgraduate specialty programs could be improved...

...family physicians in particular need to keep up to date.

It is also important that the College of Family Physicians of Canada integrate genetic knowledge and services into its objectives and examinations. Family physicians are the primary medical contact for most Canadians, and advances in genetics have significant clinical implications for their practices.

Genetics should be ranked as a higher priority in continuing medical education.

The rapid advances in medical knowledge and technologies are resulting in an ever-increasing need for continuing medical education. Maintaining physician competence is a growing priority to a variety of accreditation and licensing bodies. So far, medical genetics has not been identified as a primary area of interest by either the physicians seeking continuing education or the groups delivering the programs. This is probably because they do not fully appreciate the clinical relevance of genetic knowledge. Physicians are primarily interested in continuing education courses they see as having direct practical application to their practices.

Although awareness of the role of genes in disease is growing, our ability to use the related technologies as diagnostic or therapeutic tools is still limited. But the applications are increasing. The implications of the rapid growth in genetic information and technologies deserve to be made a higher priority in continuing medical education. As is the case at other levels of education, genetic knowledge and its applications should be included in the continuing education programs on different specialties and diseases rather than offered in separate genetics courses.

Strong liaison is needed between faculty members and the deans, chairs, and curriculum committees at Canadian medical schools.

Bringing about these changes and achieving full integration of human genetics into all aspects of medical education will require strong liaison between the medical genetics faculties and the deans, chairs, and curriculum committees of medical schools. The Canadian College of Medical Geneticists, the Association of Canadian Medical Colleges, and the American Society of Human Genetics also have valuable roles to play. They can help by identifying problems, recommending changes, and assisting in the development of curriculum objectives, teaching aids, and examination questions.

Genetics Associates

More training programs are needed to meet the demand for genetics associates.

Genetics associates are important members of the team required to deliver genetic health services efficiently. Although the need for trained genetics associates continues to grow, there is only one training program in Canada (at McGill University), and that program has fewer than 10 graduates each year. Canadian medical faculties and accredited genetic centres should consider offering additional training programs, and provincial governments should consider funding them.

7. RESEARCH

Molecular genetics provides new tools to investigate the processes of health and disease.[159] In addition to the potential for health care applications, these technologies could foster the development of a world-class Canadian biotechnology sector. The research required to realize these benefits will be a major focus of national and international activity for a long time to come.

Considerable research is needed to realize the potential health care and commercial opportunities of genetic knowledge.

There are numerous areas in which Canadian researchers can contribute, including:

- development of better methods for cloning and sequencing DNA and better computer capability for handling sequence data;
- contribution to the international effort to map and sequence the human and other genomes;
- identification of the physiological role of particular human genes and of the significance of the silent stretches of DNA between genes;
- correlation of genes and their expression;
- clarification of the biological processes underlying health and disease;
- investigation of the degree and origin of genetic variation in Canadian populations and of clustering of genes in certain populations;
- development of diagnostic and treatment technologies for specific genetic diseases and mutations;
- research on identification and control of mutagens.

There are many priority areas for research, including investigation of mutations that are specific to Canadian populations.

There are several specific reasons for Canadians to be involved in genetic research. As a consequence of immigration and settlement patterns, some diseases and mutations occur with higher than average frequency in certain regions of the country or subgroups of the population. Research is needed to identify these mutations and to develop solutions to health problems of particular concern to Canadians.

In addition, Canada could benefit from the health, biotechnology, and commercial opportunities that will arise nationally and internationally from the genetic technologies.

"Big" versus "Small" Science

Development of human gene maps and genome sequences is "big science" and requires international cooperation and extensive effort, time, and money. As the rate of mapping and sequencing accelerates, the critical chore of accessing current information will become more difficult. However, several countries are now in the process of forming the Human Genome Organization (HUGO), an international body for coordinating human genome mapping and information. HUGO will aid international efforts by, for example:

Gene mapping and sequencing involve international cooperation.

- providing common systems to facilitate international transfer of data;
- developing consistent reporting formats; and
- assisting in the collection, storage, and distribution of DNA clones and human cell lines.

The organization and funding of genome mapping and sequencing have sparked vigorous debate in the United States, Japan, England, and France.[160] Despite the importance of the information generated, there is concern that the funding of such "big science" projects will siphon money away from

independent "small science" research. New approaches, such as sequence-tagged-sites mapping, provide "small" and "big" players with equal opportunity to participate in the mapping project.

Canadian Participation

Canada has made significant contributions to genetics research.

Canada has been a major contributor to genetic research, primarily in identifying the role of specific genes and gene-disease relationships, and in developing effective screening and treatment technologies for genetic diseases. Most of the genome mapping work is being done in the United States, Japan, and Europe, but Canadian scientists have played and are continuing to play an important part in this international effort. Our contributions are based not on large mapping and sequencing programs, but rather on investigating those portions of DNA where mutations are found with high frequency in Canadian populations. Canadian studies of families with certain genetic diseases have provided valuable information. Canada has world-class research teams and research centres, and exceptional competence in data storage and analysis. Canadian researchers are currently at the forefront in the investigation of such important diseases as Duchenne muscular dystrophy, cystic fibrosis, hypercholesterolaemia and Huntington disease.[161]

A network on genetics of human diseases has been established in the National Centres of Excellence Program.

The Canadian government recently acknowledged the importance of human genetics research in Canada by establishing a network called "Genetic Basis of Human Disease: Innovations for Health Care" in the National Networks of Centres of Excellence Program.[162]

Underfunding

Despite the infusion of new research funds in the National Centres of Excellence Program — including $17 million over four years for genetics research — medical research in Canada is chronically underfunded.[163] Whether expressed in absolute dollars, or as a percentage of gross national product or per capita contribution, Canadian allocations to medical research fall significantly below expenditures in other developed countries.[164] Underfunding has a particularly negative impact on new areas of research, on individuals early in their research careers, and on research that requires sophisticated equipment or technology. Molecular genetics research is vulnerable on all three counts. These resource limitations hamper our progress in resolving important health problems.

Underfunding is hampering progress in solving important health problems.

In 1988-89, an estimated $400 million was allocated to health sciences research in Canada.[165] This total includes funds from federal and provincial governments and from voluntary agencies and foundations. The relevant private sector allocations are not known but may constitute an additional 10 per cent. The Medical Research Council (MRC) is the single largest source of medical research funding in Canada, providing $190 million, or 48 per cent of the total, in 1988-89.

The proportion of medical research funds spent on genetic research in Canada is small.

The proportion of medical research funds spent on genetic research in Canada is small, but the precise amount is difficult to determine. In the case of the MRC, this is because much of the relevant funding is allocated through MRC granting committees other than the genetics or molecular biology and

biochemistry committees. In 1988-89, the genetics review committee approved grants of $3.8 million (3.5 per cent of all research grants) and the molecular biology and biochemistry committee approved grants of $16.2 million (12.5 per cent of total grants). Over the past five years funding levels for molecular biology and genetic research have increased slightly.[166]

The MRC awards funds to applicants on the basis of excellence of the research proposal and past performance of the researcher. It rarely targets specific research topics. It is important to maintain basic research, which has accounted for some of the major advances in medicine, but there is also a legitimate need for targeted research; and there are areas in genetics-related research that warrant targeting.

Both basic and targeted research are necessary.

Finally, innovative approaches, including group and program grants and research networks, foster the establishment of research teams and provide opportunities for coordinated research that is multidisciplinary and multitechnological in nature.

Private Sector Biotechnology Research

In 1986, 52 biotechnology companies — 30 per cent of all Canadian firms involved in biotechnology — undertook research and development in the area of health care.[167]

As a consequence of Bill C-22, investment in one relevant area — drug-related research and development in Canada — is growing. In 1988, 57 patented drug firms reported a total R&D expenditure of $164.5 million.[168] Much of the research involved participation of universities, medical schools, research teams, and networks. A Pharmaceutical Manufacturers Association of Canada survey of 47 of its members indicated that investment in R&D increased from 4.9 per cent of sales in 1987 to 6.4 per cent in 1988; the industry goal is 8 per cent by 1991, and 10 per cent by 1996.[169]

However, among the 30 biotechnology companies that responded to a 1989 Science Council survey, fewer than 10 were active in development of specific diagnostic or therapeutic products for genetic diseases.[170] Those firms that were active focused on the more common single-gene and multifactorial disorders, including cystic fibrosis, thalassaemias, muscular dystrophy, haemophilia, dwarfism, dementias, cancers, and cardiovascular disease. Most of the research on the relevant drugs is undertaken by large multinational firms. This is a reflection of the time (9-12 years) and investment (an estimated $200 million) required to bring a new drug to market.[171]

Few private sector firms are involved in developing specific diagnostic or therapeutic products for genetic diseases.

Firms cited various reasons for the relatively low rate of private sector research activity in gene-disease diagnostics and therapeutics, including:

- a lack of available funding, particularly venture capital funding;
- the fledgling state of scientific knowledge on gene-disease relationships;
- inadequate patent protection;
- uncertainty regarding possible regulatory changes affecting diagnostic and therapeutic products;
- uncertain market demand; and
- potential public concerns over ethical issues related to genetic technologies.

There are several reasons for the low rate of private sector research.

Various mechanisms could enhance the level of private sector research.

The biotechnology firms identified mechanisms that they believed would enhance the level of private sector research. Chief among these were tax credits for investors, tax credits for firms, increased direct funding, and better patent protection. Part of the solution would involve more business and entrepreneurial training for university science students. In addition, more assistance in the areas of marketing, financing, and management should be available to scientists and small firms at the start-up level.

More publicly funded research would better delineate gene-disease links and pave the way for private sector involvement. There is also a need for some fundamental market development work, specifically to raise the awareness of governments, physicians, and individuals of the potential benefits of genetic diagnostics and therapeutics. If a market exists and the basic scientific knowledge is available, the private sector will develop appropriate products.

Research Guidelines

Research guidelines should be widely distributed and adopted.

There is a need for wider awareness, discussion, and adoption of guidelines and review procedures to ensure that proposed research projects incorporate safety and ethical considerations and do not pose a risk to the human participants or the environment. In addition to the existing national guidelines for use of recombinant DNA technology, there are MRC guidelines dealing with human experimentation and somatic cell gene therapy research.[172] Only MRC-funded researchers must follow the MRC guidelines, although other research funding organizations such as the Natural Sciences and Engineering Research Council and some hospital research and ethics committees have chosen to adopt them. It would be desirable if all researchers in these fields did so.

The existing guidelines indicate respect for the potential hazard to humans associated with genetic research. Researchers and policy makers alike recognize that the continued development of guidelines, and if necessary regulations, will be essential as human genetic research evolves. The recently established National Council on Biomedical Ethics will assist in ensuring that effective review procedures and appropriate guidelines and protocols are in place to cover medical research in Canada.

AFTERWORD

This report documents the significance of genes to the health and ill health of Canadians and outlines some of the major issues, opportunities, and problems associated with the use of genetic knowledge and technology. The Science Council believes that existing genetic knowledge can and should be used to improve delivery of health care, and that the growing understanding of the role of genes in health and disease will profoundly affect disease prevention and treatment in the future.

Effective planning and action are required immediately to integrate genetics more thoroughly into current health care delivery. Planning is also needed to lead to future beneficial applications of genetic knowledge and technologies, and to avoid potential problems. The goals and initiatives presented in the first chapter of this report provide a framework upon which effective and ethical development and delivery of genetic services can proceed. It is up to each reader — as policy maker, planner, health provider, patient — to take the next steps. We must all take appropriate action to ensure that the Canadian health care system continues to evolve as a reflection of our caring society.

APPENDIX 1
Basic Genetic Facts: DNA, Genes, and Chromosomes

- The organization, structure, and function of cells are controlled by genetic material in the nucleus of cells. The genetic material consists of molecules of deoxyribonucleic acid (DNA), which serve as an encyclopedia of genetic information.

- The DNA molecules are made up of chains of nucleotides bound together in a double helix. The chains are made up of sequences of four nitrogen bases. The two strands of the DNA molecules are held together by weak bonds between the bases.

- In human beings DNA is organized into 23 pairs of chromosomes. One chromosome of each pair comes from the father and one from the mother. With the exception of the pair of sex chromosomes, the members of a chromosome pair are similar to each other in appearance and possess the same sequence of genes along their length.

- A gene is a specific stretch of the DNA molecule that codes information to translate into a specific protein. In human beings it is estimated that there are 50 000 to 100 000 genes located along the chromosomes.

- It is the specific linear sequence of nucleotides that provides the code of instructions for protein production. The number of nucleotide pairs in a gene can vary from 2000 to two million.

- Only 1 to 3 per cent of the DNA codes for proteins. The purpose of the remaining DNA is not well known, but other DNA functions include copying and transcribing genetic information, and turning genes on and off.

- The genetic message in the DNA is transferred from the nucleus to the cell protoplasm, where the protein is constructed. When the protein is formed, the gene message has been "expressed."

- An individual's full complement of DNA is referred to as his or her genome and is normally identical in the nucleus of every cell in the human body.

- In the process of sexual reproduction, the DNA divides and each parent contributes one-half the genetic complement of the offspring via the egg or sperm. The process of cell division provides ample opportunities for exchanges in the nucleotide sequences. These exchanges are one cause of mutations.

APPENDIX 2
Recombinant DNA Technologies

Recombinant DNA technologies are based on: cleavage of DNA into specific fragments; construction of recombinant DNA molecules; multiplication (cloning) of DNA; and separation and "visualization" of DNA fragments.

- Cleavage of DNA into specific fragments became possible with the discovery of restriction endonucleases, naturally occurring enzymes found in bacteria. The enzymes have the function of recognizing specific nucleotide sequences in the DNA molecule and cutting DNA at particular sites, resulting in fragments of different lengths. Each restriction enzyme, and over 400 have been identified to date, produces characteristic fragments. In addition, as a consequence of natural variations in DNA, specific fragments may vary in length between individuals. These different forms of the same fragment are called restriction fragment length polymorphisms (RFLPs).

- Different methods are available to separate an individual's DNA fragments prior to analysis. For example, because the fragments are of different lengths, a gel matrix and an electrical field (electrophoresis) can be used to generate characteristic patterns.

- Single-stranded DNA fragments, produced by cleaving DNA, can recombine when complementary fragment ends anneal through the process of base-pairing.

- Thousands (even millions) of copies of a specific fragment can be produced by inserting it into the DNA of unicellular organisms such as bacteria, viruses, or yeast, and then culturing the organism. An unlimited number of copies of specific small segments of DNA can also be made by polymerase chain reaction.

Recombinant DNA technologies have numerous applications in diagnosis of disease and carrier detection. The technologies can be used to analyse the DNA of an individual to determine whether a specific known mutation is present, or to locate and identify genes responsible for specific single-gene or multifactorial disorders. The technologies can also be used to develop libraries of cloned DNA fragments, and to aid in gene mapping and sequencing.

To analyse DNA for the presence of a known mutation involves the use of a probe. A probe is the specific DNA sequence of a known mutation that has been cloned, denatured (made single stranded), and labelled using radioactive material or biotin. Using the Southern Blotting method, single-stranded DNA fragments from the individual are separated by electrophoresis and transferred onto a nitrocellulose filter. Probe material is added and will hybridize (bind) with complementary DNA sequences on the filter. Probe DNA that does not bind can be washed away. The probe material permits "visualization" of the

probe-fragment hybrids. For example, an x-ray film placed over the filter will show darkened bands where DNA has hybridized with radioactively labelled probe material.

When the precise mutation causing a disease is not known, RFLP patterns can be used to compare the DNA of the individuals with the disease to that of individuals without disease. The gene causing the disease may be linked with a specific polymorphism. Finding such linkages will help localize the genes for specific diseases and can provide markers.

More detailed descriptions of the recombinant technologies and their applications can be found in the source documents provided below.

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APPENDIX 3
Genetic Screening Programs in Canada

Genetic screening programs are in place in all provinces and territories; they demonstrate that genetic knowledge and technology can be used, within Canadian health care systems, to prevent and treat disease.

Canada has been a pioneer in the development, evaluation, and delivery of genetic screening programs. For example, the Quebec health care system was the first in the world to offer screening for congenital hypothyroidism as a universal service.

Genetic screening serves three purposes:

1. early detection, diagnosis, and treatment of disease (the primary goal);
2. provision of reproductive options to individuals at risk for having children with serious genetic disorders;
3. clinical and epidemiological research.

Screening programs should be appropriately evaluated. Decisions to offer specific screening programs should be based on consideration of the incidence and health implications of the disorder, and the cost and effectiveness of both the screening program and follow-up treatments. All screening programs that become routine health care services in Canada are preceded by pilot studies to evaluate their effectiveness. Screening programs should be offered as part of a continuum of genetic services that includes diagnosis, counselling, and treatment.

The number of disorders for which screening programs are available is still small, but will likely grow in response to improvements both in the technology to screen for and diagnose genetic disorders, and in the options for effectively preventing and treating genetic disease.

The majority of screening programs currently offered in Canada are for newborns. In addition, there are a few programs targeted to specific populations at risk for certain serious recessive disorders to help identify adolescent or adult carriers.

At present there are no programs in Canada to screen for individuals with, or susceptible to, multifactorial diseases. Similarly, there are no workplace programs in place to screen potential employees for genetic susceptibility to disease, or to monitor employees for mutations or disease onset resulting from workplace exposures.

Neonatal Screening and Related Services
Neonatal screening programs are used primarily to assist in early diagnosis to enable early medical intervention and improved prognosis. The programs vary among provinces. The tables indicate neonatal screening programs in Canada and the location of screening laboratories and follow-up centres. Tests for a number of other disorders are available but are not offered on a widespread basis because of doubts as to their benefits and cost effectiveness.

Adult/Adolescent Carrier Screening
These programs screen for carriers of single genes that when present in a double dose cause fatal diseases for which no successful treatments are currently available. The programs are often targeted to a specific community or population in response to high incidence of a disorder. Few such programs are in place in Canada. Well-established programs include screening for Tay-Sachs disease carriers in Toronto and Montreal, and for carriers of thalassaemia in Montreal.

Table 1
Neonatal Screening Programs by Province

Neonatal screening services are provided by the health ministries of the provinces and territories. Screening and follow-up for newborns in the Northwest Territories and Yukon is done in British Columbia, Alberta, Manitoba, and Quebec on the basis of proximity; the specific tests undertaken depend on which province does the screening. Participation in neonatal screening is voluntary; in all provinces and territories parents have an option to refuse.

	BC	Alta	Sask	Man	Ont	Que	NB	NS	PEI	Nfld
Blood Tests										
Phenylketonuria	■	■	■	■	■	■	■	■	■	■
Congenital hypothyroidism	■	■	■	■	■	■	■	■	■	■
Aminocidopathies[1]		■		■		■[2]				■
Galactosaemia	■			■						
Congenital adrenal hyperplasia				■						
Biotinidase deficiency	■[p]			■[p]						■[p]
Duchenne muscular dystrophy				■[p]						
Urine Tests										
Aminocidopathies (other than PKU)				■[3]		■[3]				
Neuroblastoma						■[p]				

1. Alberta, Manitoba, and Newfoundland do general screening based on blood amino acid chromatography. Amino acid disorders that can be detected include maple syrup urine disease, tyrosinaemias, and hypermethionaemias.
2. Quebec has developed and offers a screening program for tyrosinaemia 1, because of the relatively high incidence of the disorder, particularly in the Chicoutimi region.
3. Screening for methylmalonic aciduria is available to parents in Quebec and Manitoba. Parents are asked to send dried urine samples on filter paper when the infant is two to three weeks of age. In Quebec, 94 per cent of families with newborns have chosen to participate; in Manitoba the figure is 85 per cent.

p. pilot project

Table 2
Organization of Neonatal Screening Programs in Canada: Laboratories and Follow-up Centres

SCREENING LABORATORIES	FOLLOW-UP CENTRES
B.C. C.H. Wills Laboratory, B.C. Children's Hospital, Vancouver	VANCOUVER - B.C. Children's Hospital
ALBERTA University of Alberta Hospital, Edmonton	EDMONTON - University of Alberta Hospital CALGARY - Alberta Children's Hospital
SASKATCHEWAN Provincial Laboratory, Regina	SASKATOON - Alvin Buckwald Centre
MANITOBA Cadham Provincial Laboratory, Winnipeg	WINNIPEG - Health Sciences Centre, Children's Hospital
ONTARIO Special Laboratory Services Branch, Ministry of Health, Toronto	TORONTO - Hospital for Sick Children LONDON - War Memorial Children's Hospital KINGSTON - Queen's University HAMILTON - McMaster University Medical Centre OTTAWA - Children's Hospital of Eastern Ontario
QUEBEC Centre Hospitalier de l'Université Laval (Blood screening) Centre Hospitalier de l'Université de Sherbrooke (Urine screening)	QUEBEC - Centre Hospitalier de l'Université Laval SHERBROOKE - Centre Hospitalier de l'Université de Sherbrooke MONTREAL - McGill University & Montreal Children's Hospital MONTREAL - Hôpital Ste-Justine CHICOUTIMI - Hôpital de Chicoutimi
NEW BRUNSWICK St. John Regional Hospital, St. John	ST. JOHN - St. John Regional Hospital Not centralized in other areas
NOVA SCOTIA Biochem Labs, Izaak Walton Killam Hospital, Halifax (PKU) D.J. MacKenzie Labs, Victoria General Hospital, Halifax (CH)	HALIFAX - Izaak Walton Killam Hospital for Children
P.E.I. Izaak Walton Killam Hospital, Nova Scotia (PKU) Queen Elizabeth Hospital, Charlottetown (CH)	Follow-up is done in Nova Scotia.
NEWFOUNDLAND Janeway Child Health Centre, St. John's (PKU) Health Science Centre, St. John's (CH)	ST. JOHN'S - Janeway Child Health Centre
N.W.T. AND YUKON Screening and follow-up are done in nearest province (B.C., Alberta, Manitoba, or Quebec).	

CH = congenital hypothyroidism
PKU = phenylketonuria

Sources: P. Ferreira, "Current Canadian Newborn Screening Practices," *Paediatric Medicine Quarterly* 3, no. 4 (September 1989): 111-120;
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Table 1 was adapted, with minor variations, from the article by P. Ferreira.

APPENDIX 4
Recommendations on Prenatal Diagnosis and Genetic Screening, The Royal College of Physicians of London

1. Genetic screening and prenatal diagnosis services should be equally available to the whole community. They should be recognised as an intrinsic component of maternal and child health services. *Equity in health care*

2. A policy advisory structure should be set up to facilitate decision making in the future. *Policy advisory structure*

3. Although there is clear majority support for the principles of prenatal diagnosis, some serious ethical issues are involved. A professional code of practice governing genetic screening should be developed. It should be widely publicised to reassure the public that: *Code of practice*

   a prenatal diagnosis will not be used for a positive eugenic policy;

   b prevention programmes will not detract from the appreciation of, and provision for, people with disabilities.

4. Resources should be made available: *Resources*

   a to ensure equitable delivery of existing services;

   b to support the development, evaluation and early application of new approaches.

5. Professional training in medical genetics and the principles of genetic counselling should be provided for all maternal and child health workers (GPs, obstetricians, paediatricians, family planners, health visitors and midwives). Official contact should be made with the relevant professional bodies to develop the genetic component of the training curriculum and to organise updating courses for existing practitioners. *Professional training*

6. Because of the large numbers involved, and the relative simplicity of some issues in large-scale screening programmes, genetic information and counselling must be provided at the community level. The ideal professionals to provide information and counselling would be specially trained health visitors and midwives, who are already the point of first and most frequent contact with mother and child. The suggestion is consistent with current proposals to train nurse specialists, who in this case would act as reference and training resources for MCH [maternal and child health care] workers in general. *Information and counselling*

Specialist genetic counsellors

7. Specialist genetic counsellors already work with clinical geneticists and with specialists in particular disorders. Equivalent specialist counsellors should be attached to each obstetric unit practising prenatal diagnosis. It is urgent to define a career structure for such specialist counsellors, who may have differing professional backgrounds, and carry out a wide range of activities.

National organisation

8. a Policy formulation, defining a career structure for genetic counsellors, development and distribution of educational materials and service monitoring, should be organised at the national level.

Regional organisation

b Each region needs to develop an organisation for ensuring delivery of genetic screening and prenatal diagnosis. This organisation should include clinical genetics and fetal medicine centres, neonatologists and paediatric pathologists, obstetric and paediatric consultants, primary care physicians, community physicians, health workers involved in family-planning, health visitors, midwives, nurses, and experts in health education and community medicine.

District organisation

c For the service to be delivered effectively, the regional organisation must have roots at the district level, in the antenatal clinics and among general practitioners and other maternal and child health workers.

District and regional co-ordinators

9. Because of their multidisciplinary nature, prenatal diagnosis services should be under the overall supervision of designated district and regional co-ordinators who may often, but not always, be clinical geneticists. The co-ordinator's responsibility should be to ensure that the services are provided to the recommended standard and co-ordinated and monitored throughout each region.

National audit

10. Though monitoring should be organised on a regional basis, a national centre is needed to develop appropriate methods, co-ordinate information nationally, and stimulate equal service delivery throughout the country.

Genetic health education

11. Face-to-face counselling and written information are complementary rather than alternative sources of information for an educated population; one should not be given without the other. Information packages need to be directed to schools, young couples and pregnant women, and individuals with defined genetic risks. Because of the wide range and different levels of educational resources needed to cover the spectrum of potential abnormalities, a National Genetic Health Education Unit is needed to generate, store and disseminate information.

Implementation

12. These proposals should be implemented through working groups and supported by the DoH [Department of Health].

Source: *Prenatal Diagnosis and Genetic Screening: Community and Service Implications*, The Royal College of Physicians of London, September 1989.

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BOX NOTES

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Box 7

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Box 8

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Box 9

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PROJECT PARTICIPANTS

Steering Committee

Chairman
Charles R. Scriver*

Members
Patricia Baird
Head
Department of Medical Genetics
Faculty of Medicine
University of British Columbia
Vancouver, British Columbia

Monique Bégin
Joint Chair
Women's Studies
Carleton University and University of Ottawa
Ottawa, Ontario

J. Donald Hatcher
Dean Emeritus
Faculty of Medicine
Dalhousie University
Halifax, Nova Scotia

Neil A. Holtzman
Professor
Department of Pediatrics
Johns Hopkins University
Baltimore, Maryland

Geraldine A. Kenney-Wallace*
(ex officio)

Nuala Kenny (until January 1989)
Head
Department of Paediatrics
Dalhousie University
Halifax, Nova Scotia

Bernard M. Leduc*

Stuart L. Smith
President
RockCliffe Research and Technology Inc.
Ottawa, Ontario

Jennifer M. Sturgess*

Vaira Vikis-Freibergs (ex officio)
(until December 1988)
Vice-Chairman
Science Council of Canada

Joan Watson
President
Joan Watson Enterprises Ltd.
Toronto, Ontario

John M. Webster*

Member and Project Officer
Katherine Arkay
Science Adviser
Science Council of Canada

Project Staff
Cara Westcott (until September 1989)
Research Associate
Science Council of Canada

* Member of Council

Subcommittees

Science, Technology, Services

Chairman
Jennifer M. Sturgess*

Members
Claude Laberge
Faculté de médecine
Université Laval
Québec (Québec)

Charles R. Scriver*

Louis Siminovitch
Director
Mount Sinai Hospital Research Institute
Toronto, Ontario

Ronald G. Worton
Geneticist-in-Chief
Hospital for Sick Children
Toronto, Ontario

Ethics-Legal

Chairman (1989-90)
Bartha Knoppers
Professeure
Faculté de droit
Université de Montréal
Montréal (Québec)

Chairman (1987-89)
Nuala Kenny
Head
Department of Paediatrics
Dalhousie University
Halifax, Nova Scotia

Members
Bernard Dickens
Professor of Law
University of Toronto
Toronto, Ontario

Abbyann Lynch
Director
Westminster Institute for Ethics and Human Values
London, Ontario

Noreen Rudd
Geneticist
Alberta Children's Hospital
Professor
Paediatrics and Obstetrics
University of Calgary
Calgary, Alberta

Dorothy Wertz
School of Public Health
Boston University
Boston, Massachusetts

Education

Chairman
J. Donald Hatcher
Dean Emeritus
Faculty of Medicine
Dalhousie University
Halifax, Nova Scotia

Members
Dale W. Dauphinee
Director
Continuing Medical Education
Professor
Faculty of Medicine
McGill University
Montreal, Quebec

John Hamerton
Head
Department of Human Genetics
University of Manitoba
Winnipeg, Manitoba

Alexandra Harrison
Director
Educational Services
Canadian Medical Association
Ottawa, Ontario

Robert Maudsley
Vice Dean
Faculty of Medicine
Queen's University
Kingston, Ontario

* Member of Council

Statistics, Epidemiology

Chairman
Joan Watson
President
Joan Watson Enterprises Ltd.
Toronto, Ontario

Members
Patricia Baird
Head
Department of Medical Genetics
University of British Columbia
Vancouver, British Columbia

Philip Banister
Senior Medical Consultant
Health Services and Promotion Branch
Health and Welfare Canada
Ottawa, Ontario

David Bray
Director
Health Division
Statistics Canada
Ottawa, Ontario

Neil A. Holtzman
Professor
Department of Pediatrics
Johns Hopkins University
Baltimore, Maryland

Economics

Chairman
Monique Bégin
Joint Chair
Women's Studies
Carleton University and University of Ottawa
Ottawa, Ontario

Members
Orvill Adams
Director
Economics Branch
Canadian Medical Association
Ottawa, Ontario

Jane Fulton
Professor
Faculty of Administration
University of Ottawa
Ottawa, Ontario

Leonard Pinsky
Director
Centre for Human Genetics
McGill University
Montreal, Quebec

Individuals and Organizations Consulted

The following individuals and organizations were among those consulted in the course of the Science Council project on genetics. The participation of individuals listed varied from advice regarding project design, to technical input, to policy advice, to review of this report. Regretably, the list is incomplete; it would be impossible to name every individual who made a contribution.

The Science Council and project steering committee thank all those who contributed for their valuable assistance and advice, including Joan Watson and Paul Tindall for their contributions to the writing of the report and summary documents.

Research, Health, and Science Policy

Douglas Angus, Community Health and Epidemiology, Queen's University
Carol Bocchinni, McKusick Data Base, Johns Hopkins University
Carol Clow, Montreal Children's Hospital
Ursula Dawe, Alberta Children's Hospital
Robert Evans, Department of Economics, University of British Columbia
David Feeney, Department of Clinical Epidemiology and Biostatistics, McMaster University
Mary Fujiwara, Department of Epidemiology and Biostatistics, McGill University
Abby Lippman, Department of Epidemiology and Biostatistics, McGill University
Victor McKusick, Faculty of Medicine, Johns Hopkins Hospital
Ken Morgan, Department of Epidemiology and Biostatistics, McGill University
J. Fraser Mustard, Canadian Institute for Advanced Research
Lee Soderstrom, Department of Economics, McGill University
Matthew Spence, Atlantic Research Centre for Mental Retardation, Dalhousie University
Greg Stoddart, Department of Clinical Epidemiology, McMaster University
Neil Tremblay, Canadian Medical Association

Education

Arlene Burden, Canadian Association for School Health
Hélène Cameron, Education and Training Unit, Health and Welfare Canada
John Dirks, Faculty of Medicine, University of Toronto
Joseph D. McInerney, Biological Sciences Curriculum Study, Colorado College
Graham Orpwood, Orpwood Associates Inc., Toronto
John Parboosingh, Faculty of Medicine, University of Calgary
Vincent Riccardi, Genetics Institute, Pasadena, California
De Guise Vaillancourt, Association of Canadian Medical Colleges

Education Ministries and Biology Teachers Consulted

Education Ministries: Health Education
Barbara Esdale, Alberta
David Kelpin, British Columbia
Joyce McMartin, Manitoba
Tom Hanley, New Brunswick
Sheila Anderson, Newfoundland
Helen Balmoff, Northwest Territories
Mike Law, Nova Scotia
Barbara Johnson, Ontario
Lyle Huggan, Prince Edward Island
Ray Petrunik, Saskatchewan
Fran Berry, Yukon Territory

Education Ministries: Science Education
Philip Campbell, Alberta
David Williams, British Columbia
Evhan Uzwyshyn, Manitoba
Leo-Paul Charest, New Brunswick
Paul Munroe, New Brunswick
Harry Elliott, Newfoundland
M.S. Naidoo, Northwest Territories
Laurie Delbridge, Nova Scotia
Geraldine Connelly, Ontario
Don Norman, Prince Edward Island
Denis Chabot, Quebec
Barry Mitschke, Saskatchewan
Bill Ferguson, Yukon Territory

Biology Teachers
Gordon Jasper, Alberta
Steven Cardwell, British Columbia
Jack Burditsky, Manitoba
Sally Shannon, New Brunswick
Gerard Hilliard, Newfoundland
Russ Connors, Northwest Territories
Patricia Betts, Nova Scotia
Sylvia Fullan, Ontario
Leigh Ramsay, Prince Edward Island
Jean-Claude Benoit, Quebec
Dianne Swenne, Quebec
Barry Minchkie, Saskatchewan
Lee Kobica, Yukon Territory

Undergraduate Genetics Education

David Nash, Department of Genetics, University of Alberta

Health Care-Related Training Programs

Pharmaceutical Science Programs
John Bachinsky, University of Alberta
James Blackburn, University of Saskatchewan
Gerald Duncan, Memorial University of Newfoundland
Patrick Farmer, Dalhousie University
Gaston Lebrecque, Université Laval
John McNeill, University of British Columbia
Donald Plevier, University of Toronto
John Steele, University of Manitoba

Medical Education

American Society of Human Genetics
Association of Canadian Medical Colleges
College of Family Physicians of Canada
Medical Council of Canada
Royal College of Physicians and Surgeons of Canada

Notes:
1. In the course of the project, genetics education was discussed with geneticists at all Canadian medical schools.
2. Because an extensive survey of genetics education in North American medical schools was conducted recently by the American Society of Human Genetics, a separate survey was not conducted.

Ethical and Legal Issues

Claire Bernard, Lawyer/Consultant, Montreal
Charles Black, Canadian Life and Health Insurance Association
Mark Daniels, Canadian Life and Health Insurance Association
John Fletcher, Department of Medicine, University of Virginia
Derek Jones, Law Reform Commission, Montreal
Annette Lefebvre, Consultant, Montreal
Lori Luther, Consultant, Montreal
Angus McLaren, Department of History, University of Victoria
Judith Miller, National Council on Bioethics in Human Research
Benno Müller-Hill, Cologne University, Federal Republic of Germany
Michèle Rivet, Law Reform Commission, Montreal
Sanda Rodgers, Faculty of Law, University of Ottawa
William Seidelman, Faculty of Medicine, McMaster University
Carole Tremblay, Consultant, Montreal
Panel and participants in health workshop of the conference Ethical Choices in the Age of Pervasive Technology, October 1989, Guelph, Ontario

Provincial and Territorial Health Ministries

Connie Becker, Maternal and Child Health, Manitoba Department of Health
Garry Curtis, Policy, Planning and Legislation, British Columbia Ministry of Health
Alan Davidson, Health Services Branch, Yukon Department of Health and Human Resources
Omer Doiron, Public Health and Medical Services, New Brunswick Department of Health and Community Services
Wayne Fritz, Public Health Economics Branch, Saskatchewan Department of Health
F. Ian Gilchrist, Department of Health, Government of the Northwest Territories
Greg Hammond, Cadham Provincial Laboratory, Manitoba Department of Health
Kevin Hogan, Community Health, Newfoundland Department of Health
D.J. Junk, Policy and Planning Services Division, Alberta Health
Roch Khazen, Public Health Branch, Ontario Ministry of Health

Betty Macdonald, Health Surveillance Registry, British Columbia Ministry of Health
Ella Macleod, Division of Nursing, Prince Edward Island Department of Health and Social Services
Patricia Ngan, Vital Statistics Division, British Columbia Ministry of Health
Mary Scott, New Brunswick Department of Health and Community Services
François Simard, Ministère de la santé et des services sociaux
Ron Strohmaier, Data Management Branch, British Columbia Ministry of Health
Wayne Sullivan, Community Health Programs, Nova Scotia Department of Health and Fitness
Alan Thomson, Hospital Programs, British Columbia Ministry of Health
Karen Titanich, Advisory Committee on Genetic Services, Alberta Health
Glenda Yeates, Policy and Health Economics Branch, Saskatchewan Department of Health

Federal Ministries

Patricia Birkwood, Bureau of Radiation and Medical Devices, Health and Welfare Canada
A.J. Clayton, Federal Centre for AIDS, Health and Welfare Canada
Elizabeth Dickson, Biotechnology and Health Care Products, Industry, Science and Technology Canada
Peter Glynn, Social Service Programs Branch, Health and Welfare Canada
Janet Hatcher-Roberts, Policy, Communications and Information Branch, Health and Welfare Canada
Joe Hauser, Health Services and Promotion Branch, Health and Welfare Canada
Geza Hetenyi, Medical Research Council of Canada
Denise Leclerc, Health Insurance, Health and Welfare Canada
Sheena Lee, Health Services and Promotion Branch, Health and Welfare Canada
Joe Losos, Laboratory Centre for Disease Control, Health and Welfare Canada
David Martin, Health Services and Promotion Branch, Health and Welfare Canada
Mary Mes-Hartree, Biotechnology and Health Care Products, Industry, Science and Technology Canada
Allen Murdock, Medical Services Branch, Health and Welfare Canada
Francis Rolleston, Medical Research Council of Canada
Greg Sherman, Laboratory Centre for Disease Control, Health and Welfare Canada
Lewis Slotin, Medical Research Council of Canada
John Smith, Environmental Health Directorate, Health and Welfare Canada
Bernard Starkman, Criminal Law Review, Department of Justice
Bill Tholl, Policy, Communications and Information Branch, Health and Welfare Canada
Jessie Weldon-Gibb, Technology Policies Branch, Industry, Science and Technology Canada
Mark Wheeler, Health Economics and Statistical Analysis Section, Health and Welfare Canada
Don Wigle, Laboratory Centre for Disease Control, Health and Welfare Canada

Disease Experts

Manuel Buchwald (cystic fibrosis), Department of Genetics, Toronto Hospital for Sick Children
Webster Cavenee (retinoblastoma), Ludwig Institute for Cancer Research, Montreal
Bernice Cohen (chronic obstructive pulmonary disease), Department of Epidemiology, Johns Hopkins University
Leigh Field (diabetes mellitus), Medical Genetics, Alberta Children's Hospital
Michael Hayden (Huntington disease), Department of Medical Genetics, University of British Columbia
Keith Isenberg (schizophrenia), Washington University Medical Center, St. Louis, Missouri
Mary-Claire King (breast cancer), School of Public Health, University of California (Berkeley)
Estelle LaMothe (autosomal dominant polycystic kidney disease), Division of Medical Genetics, McGill University
David Lillicrap (factor VIII deficiency), Department of Pathology, Richardson Laboratory, Queen's University
Daniel Nebert (lung cancer), National Institutes of Health, Bethesda, Maryland
David Rosenblatt (autosomal dominant polycystic kidney disease), Division of Medical Genetics, McGill University

Peter St. George-Hyslop (Alzheimer disease), Neurogenetics Laboratory, Massachusetts General Hospital
Joellen Schildkraut (ovarian cancer), Department of Epidemiology, University of North Carolina
Ann Smith (cystic fibrosis), Children's Hospital of Eastern Ontario
Sandra Wolman (familial polyposis coli), Cancer Genetics, Michigan Cancer Foundation
Raymond White (colon cancer), Howard Hughes Medical Institute, University of Utah
Roger Williams (coronary heart disease), Cardiovascular Genetics Research Clinic, Salt Lake City, Utah

Note:
Committee and subcommittee members provided information on specific diseases: Charles Scriver (thalassaemia, Tay-Sachs disease, phenylketonuria); Ronald Worton (muscular dystrophy).

Associations Representing Individuals with or at Risk for Diseases with Possible Genetic Causes

Patricia Guyda, Canadians for Health Research, Montreal

In addition, the following 47 societies participated through a survey conducted for the Science Council by Canadians for Health Research.

Alberta Heritage Foundation for Medical Research
Allergy Foundation of Canada
Alzheimer Society of Canada
Association canadienne de l'ataxie de Friedreich
Autism Society of Canada
British Columbia Lung Association
Canadian Association for Narcolepsy
Canadian Celiac Association
Canadian Cerebral Palsy Association
Canadian Cystic Fibrosis Foundation
Canadian Foundation for Ileitis and Colitis
Canadian Foundation for the Study of Infant Deaths
Canadian Friends of Schizophrenics
Canadian Geriatrics Research Society
Canadian Hemochromatosis Society
Canadian Institute of Child Health
Canadian Liver Foundation
Canadian Lung Association
Canadian Mental Health Association
Canadian Neurological Coalition
Canadian Sickle Cell Society of Quebec
Cancer Research Society Inc.
Charcot-Marie-Tooth Disease International Association, Inc.
Dystonia Medical Research Foundation (Canada)
Huntington Society of Canada
Juvenile Diabetes Foundation Canada
Kidney Foundation of Canada
Kidney Foundation of Canada (Manitoba Branch)
Learning Disabilities Association of Canada
Manic Depressive Association of Metro Toronto
Manitoba Cancer Treatment and Research Foundation
Manitoba Mental Health Research Foundation
Multiple Sclerosis Society of Canada
Muscular Dystrophy Association of Canada
National Cancer Institute of Canada
National Eating Disorder Information Centre
Neurofibromatosis Association of Saskatchewan
Neurofibromatosis Society of Ontario
Ontario Mental Health Foundation
Osteoporosis Society of Canada
Quebec Rette Syndrome Foundation
Reye's Syndrome Foundation of Canada
RP Eye Research Foundation
Saskatchewan Health Research Board
Society for Mucopolysaccharide Diseases
Spina Bifida Association of Canada
Tourette Syndrome Foundation of Canada

Canadian Medical Genetics Centres

Patricia Baird, Department of Medical Genetics, University of British Columbia
Ab Chudley, Department of Clinical Genetics, Winnipeg Children's Hospital
Louis Dallaire, Génétique médicale, Hôpital Sainte-Justine
Ron Davidson, Department of Pediatrics, McMaster University Medical Centre
S. Farrell, Department of Lab Medicine, Credit Valley Hospital
P. Ferreira, Mackenzie Health Sciences Centre, University of Alberta
H. Allen Gardner, Genetic Services, Oshawa General Hospital
Alasdair Hunter, Genetics Department, Children's Hospital of Eastern Ontario
R. Brian Lowry, Medical Genetics Clinic, Alberta Children's Hospital
Leonard Pinsky, Centre for Human Genetics, McGill University

Public Information

Canadian Science Writers' Association
Michael Dence, Royal Society of Canada, Ottawa
Lydia Dotto, Journalist, Toronto
Edna Einsiedel, School of Journalism, University of Calgary
Paul Tisdall, The Network, Ottawa

Private Sector Biotechnology Firms

The following 30 firms participated in a survey conducted for the Science Council by Ying Gravel of the HSC Research Development Corporation.

Alberta

Biomira Inc.
Synphar Labs

British Columbia

Helix Biotech Corporation
Quadra Logic Technologies Inc.
Syndel Laboratories Ltd.
Vancouver Island Antibodies Ltd.

Manitoba

ABI Biotechnology Inc.

Nova Scotia

Dominion Biologicals Ltd.

Ontario

AB Biological Supplies Inc.
Allelix Biochemicals
Allelix Diagnostics Inc.
Bocknek Ltd.
Canadian Bioclinical
Cangene Corp.
Cedarlane Lab Ltd.
Ciba-Geigy Canada Ltd.
Connaught Labs Ltd.
Cyberfluor Inc.
Eli Lilly Inc.
HSC Research Development Corporation
Hybrisens Ltd.
Joldon Diagnostics
Mann Testing Laboratories
Meiogenic Research Corp.
Ortho Pharmaceutical (Canada) Ltd.
Syntex Inc.
Waitaki International Biosciences

Prince Edward Island

Diagnostic Chemicals Ltd.

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Saskatchewan

POS Pilot Plant Corporation

MEMBERS
of the Science Council of Canada

(as of December 1989)

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Geraldine A. Kenney-Wallace, LRIC, MSc, PhD, ARIC, FRSC

Members
John M. Anderson, PhD
Vice-President, Operations
Atlantic Salmon Federation
St. Andrews, New Brunswick

Norman L. Arrison, BSc, MSc, PhD, PEng
Arrison Consultants
Red Deer, Alberta

Morrel P. Bachynski, BEng, MSc, PhD, FAPS, FCASI, FRSC, FIEEE
President
MPB Technologies Inc.
Dorval, Quebec

Richard Bolton, PhD
Directeur général
Centre canadien de fusion magnétique
Institut de recherche d'Hydro-Québec
Varennes (Québec)

Douglas Bennell Craig, BASc, PhD
Teacher and Instructor
F.H. Collins Secondary School and
Yukon College
Whitehorse, Yukon

Simon J.S.W. Curry, BA, MA, PhD
Manager
VHDL and High-Level Capture
Bell-Northern Research
Ottawa, Ontario

James Cutt, MA, PhD
Professor
School of Public Administration
University of Victoria
Victoria, British Columbia

Richard M. Dillon, BSc, LLD
Principal
Alafin Consultants Limited
Toronto, Ontario

Gerald B. Dyer, BSc
Director — Research
Du Pont Canada Inc.
Kingston, Ontario

Robert O. Fournier, BSc, MSc, PhD
Associate Vice-President (Research)
Dalhousie University
Halifax, Nova Scotia

J. Barry French, BASc, MSc, PhD, FRSC, FRSA, FCASI
Professor
Institute for Aerospace Studies
University of Toronto
Downsview, Ontario

Merritt A. Gibson, BSc, MSc, PhD
Professor and Head of the Department
Department of Biology
Acadia University
Wolfville, Nova Scotia

J.C. (Clay) Gilson, BSA, MSc, PhD, FAIC, LLD
Professor
Department of Agricultural Economics
University of Manitoba
Winnipeg, Manitoba

Gordon Gow, PhD (hon)
President and Chief Executive Officer
Ontario International Corporation
Toronto, Ontario

Robert G. Guidoin, PhD
Professeur titulaire
Laboratoire de chirurgie expérimentale
Pavillon de services
Université Laval
Québec (Québec)

Bernard M. Leduc, MD, DPhil
Chef de la direction scientifique et
directeur régional
Wyeth-Ayerst Research — Canada
Saint-Laurent (Québec)

Gerald S.H. Lock, BSc, PhD, FEIC, FCSME
Professor
Department of Mechanical Engineering
University of Alberta
Edmonton, Alberta

Ian G. MacQuarrie, BSc, MSc, PhD
Professor
Department of Biology
University of Prince Edward Island
Charlottetown, Prince Edward Island

Frank G. Marsh, BSc, BEd, MEd, PhD
President
Eastern Community College
Burin, Newfoundland

Karim Wade Nasser, PhD, PEng
Professor
Department of Civil Engineering
University of Saskatchewan
Saskatoon, Saskatchewan

John A. Roth, MEng
Executive Vice-President
Product Line Management
Northern Telecom Limited
Mississauga, Ontario

Charles R. Scriver, MD, FRSC
Professor of Pediatrics, Genetics and
Biology
McGill University
Director
deBelle Laboratory for Biochemical
Genetics
The McGill University-Montreal
Children's Hospital Research Institute
Montreal, Quebec

Jennifer M. Sturgess, BSc, PhD
Vice-President
Medical and Scientific Affairs
Parke-Davis, Warner-Lambert Canada Inc.
Scarborough, Ontario

Andrew J. Szonyi, MBA, MASc, PhD, PEng
Chairman
Zarex Management
Toronto, Ontario

John M. Webster, BSc, PhD, ARCS, DIC
Professor
Department of Biological Sciences
Simon Fraser University
Burnaby, British Columbia

Hugh Robert Wynne-Edwards, BSc, MA,
PhD, DSc, FRSC
Chief Executive Officer
Moli Energy Limited
Vancouver, British Columbia